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The headache-sleep study:

Sleep and pain thresholds in healthy controls and patients with migraine and tension type headache

Thesis for the degree of Philosophiae Doctor

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*Norsk tittel: S*øvn og smerteterskler hos friske kontroller og pasienter med migrene og spenningshodepine

«The headache sleep study"

Sammendrag:
Hodepine kan både lindres av og utløses under søvn. Videre kan man bli mer følsom for hverdagslige stimuli som lukt, lys og lyd mens man har migrenehodepine. I vår studie deltok personer med spenningshodepine, migrene og friske kontroller. Vi sammenliknet søvn- og hodepinedagbøker, en rekke spørreskjemasvar, objektiv søvn-undersøkelse (polysomnografi) og målte smerteterskler. Alle hodepinepasientene rapporterte mer angstsymptomer og subjektive søvnplager enn friske. Migrenepasienter med hodepineanfall som vanligvis starter på dagtid og spenningshodepinepasienter var som forventet hyppigere dagtrøtte, men det var uventet at de objektivt sett sov bedre enn friske kontroller. Disse hodepinepasientene opplevde tidligere smerte ved trykk og temperaturstimulering enn friske kontroller. Andre studier har vist at friske kontroller får økt søvnkvalitet og lettere utløsbar smerte etter lite søvn sammenliknet med normal søvn. I denne studien viste søvndagbøkene derimot ingen forskjell i gjennomsnittlig søvntid siste 2 uker. Migrenepasientene med hodepinestart under søvn eller ved oppvåkning, var eneste hodepinegruppe som hadde tendens til litt dårligere søvnkvalitet. Det var derfor uventet at denne gruppen *ikke* var mer dagtrøtte og *ikke* hadde lavere smerteterskler enn friske kontroller. Forklaringen kan være at disse personene lett lar seg aktivere. Ulempen kan være at søvnen lettere blir forstyrret enn hos friske. Fordelen er at de ikke føler seg særlig trøtte dagen etterpå og at de i mindre grad blir «overfølsomme». Generelt hadde migrenepasientene raskere innsovning om kvelden siste 2 dager før anfall sammenliknet med tiden mellom anfall.

Samlet sett er det argumenter for at et relativt søvnunderskudd er en medvirkende årsak til hodepine. Det kan være like riktig å si at man lettere får hodepine når man er trøtt og sliten som at man blir trøtt/søvnig før et hodepineanfall. Dessuten tyder våre data på at hodepinepasienter som får sine anfall på dagtid, trenger mer søvn enn personer uten hodepine.

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Table of Contents

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 thomography

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

vlPAG – Ventrolateral periaqueductal grey matter

VLPO – Ventrolateral preoptic nucleus

Summary in English

Background

Headache can be relieved or released during sleep, but there are few polysomnograpic (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 dagtretthet 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 dagtidstretthet 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 sever 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 to 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 caracteristics:

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. Periaquaductal gray matter (PAG) in mecencephalon, 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 fromdural 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 mecencephalic 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)

Behavioral aspects.	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.
Physiologic aspects:	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 forbrain and the ventrolateral preoptic area of hypothalamus (VLPO) during the day (McCarley, 2007). Adenosine also inhibits basal forebrain (important for arousal) and exogenly 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, serotoninergic raphe nuclei, dopaminergic ventrolateral periaquaductal gray matter (vlPAG) and histaminergic tuberomamillar 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 vlPAG (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 (Force, 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 divagating (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
Headache		
Migraine		
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)
Sleep related migraine		
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 noctural 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 migrainurs 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
Tension-type headache		
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
Migraine:		
Fernandez, 2009	Blinded cross sectional, 20 with unilateral migraine and 20 controls	Reduced PPTon 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 tholerance 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.
Preictal/ictal:		
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 migraineand TTH when headache frequency rises towards chronicization
Tension type headache:		
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.
Sleep deprived healthy controls:		
Onen, 2001	Prospective double blind cross over, total sleep deprivation, REM or SWS interuption. 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 exploreatory 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

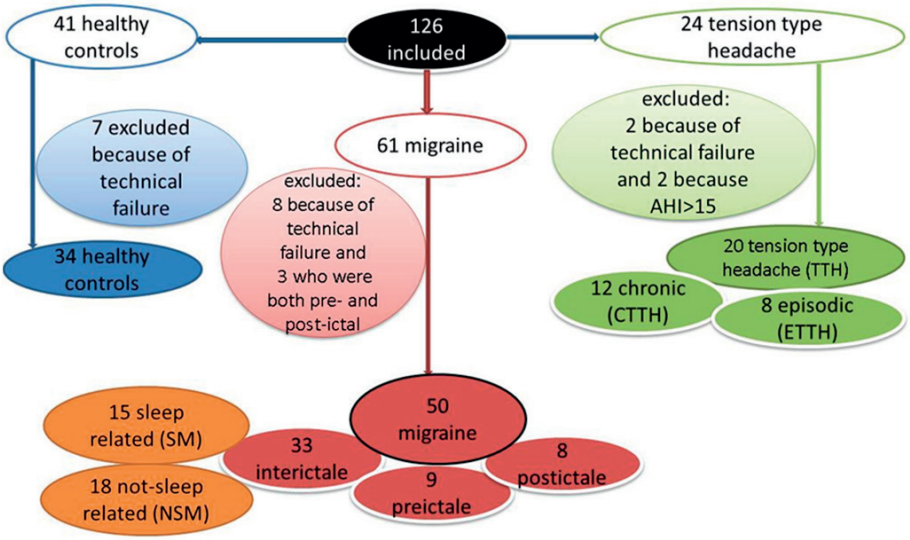
6 Design

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)

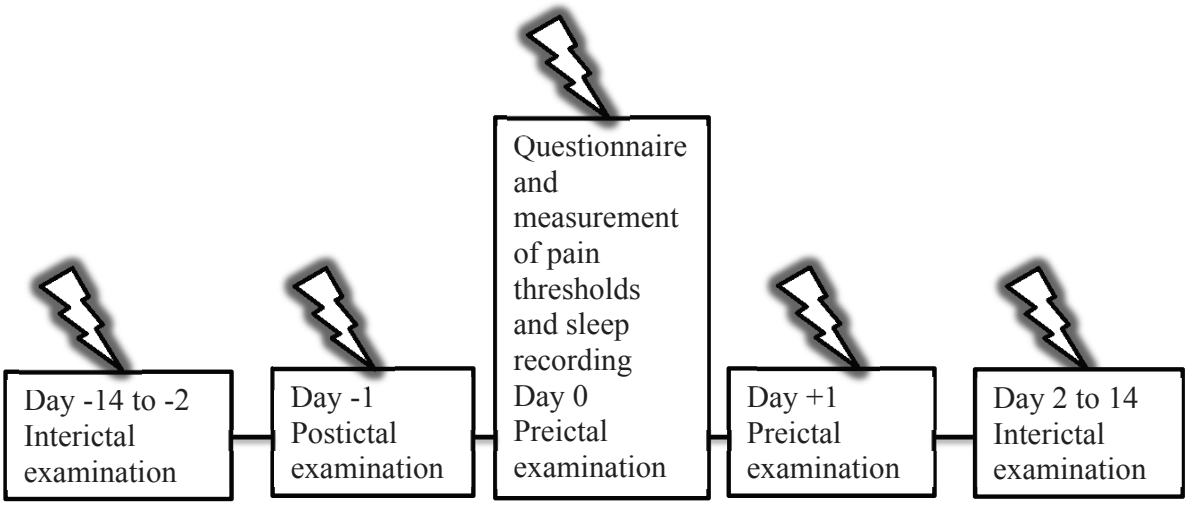
Figure 1. Participants in the headache sleep study.



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) (Engstrøm 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 PSQIgs (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**
Subjetive 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 (ºC)[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 headeache (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 parametres 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 cero" 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

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 (Force, 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" (Force, 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 divagating 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.

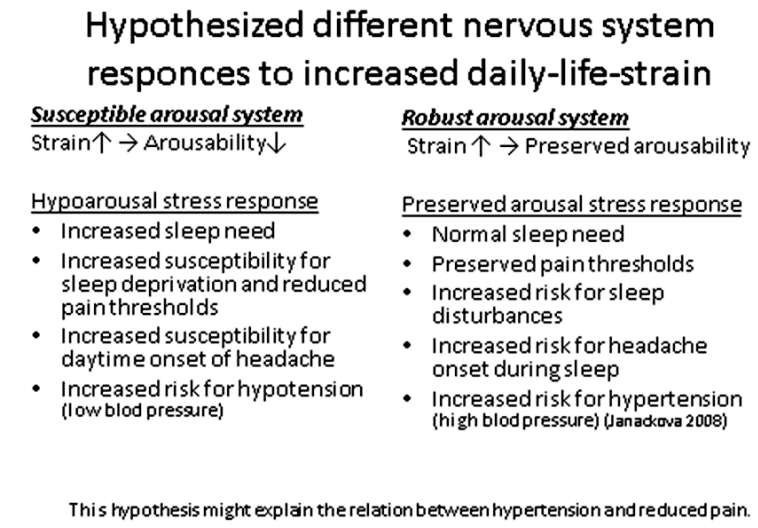
Looking ahead of sleep deprivation or not, those groups with a tendency to be "hypoaroused" (TTH and NSM groups) also tended to have reduced PT while those with preserved "arousability had preserved normal PT. If hyperarousability also is related to increased PT there is a pattern. Furthermore, arousability 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 responces 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 blod 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 blod 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 were 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.

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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)

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

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.

-	Controls[6] (n=34)	Migraine (n=33)	Sleep-migraine (n=15)	Non-sleep migraine (n=18)	Tension-type headache (n=20)
Total sleep time (min)	409 (68)	435 (61)	417 (67)	451 (52)	432 (46)
Sleep efficiency (%)	90.0 (8.1)	91.0 (6.1)	89.4 (7.6)	92.4 (4.2)	91.2 (5.6)
Awakening index (no/h)	0.99 (0.59)	1.27 (0.74)	1.45 (0.84)	1.12 (0.63)	1.1 (0.6)
WASO duration (minutes)	4.4 (3.8)	3.8 (1.7)	3.4 (1.3)	3.6 (1.6)	4.1 (2.7)
Stage 1 (min)	27 (19)	32 (15)	35 (17)	29 (13)	29 (15)
Stage 2 (min)	197 (47)	201 (44)	194 (44)	206 (45)	185 (34)
Stage 3 (min)	86 (31)	97 (28)	**88 (25)[5]**	104 (28)	**107 (21)[5]**
REM (min)	99 (26)	106 (35)	99 (38)	112 (32)	111 (30)
Fast arousal index (per hour)[1]	18.3 (5.7)	16.3 (9.1)	17.4 (8.6)	15.5 (9.7)	14.5 (4.3)
Mean fast arousal duration (seconds)	9.3 (1.1)	9.0 (1.3)	9.3 (1.5)	8.7 (1.3)	9.6 (1.2)
D-burst index (per hour)[2]	11.8 (8.0)	9.5 (7.5)	7.3 (5.7)	11.3 (8.3)	7.9 (6.3)
K-burst index (per hour)[2]	3.0 (3.8)	3.3 (2.5)	2.4 (2.2)	4.0 (2.5)	3.7 (4.5)
Pressure pain threshold (kPa)[3]	661 (249)	549 (135)	586 (141)	519 (125)	543 (191)
Heat pain threshold (°C)[4]	13.4 (3.1)	11.7 (3.6)	12.4 (3.3)	11.0 (3.8)	12.7 (3.7)
Cold pain threshold (°C)[4]	20.8 (6.3)	17.2 (6.9)	18.4 (6.3)	16.2 (7.3)	19.4 (7.4)

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

Article I

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RESEARCH ARTICLE Open Access

Sleep quality, arousal and pain thresholds in migraineurs: a blinded controlled polysomnographic study

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Abstract

Background: Our aim was to compare subjective and objective sleep quality and arousal in migraine and to evaluate the relationship between sleep quality and pain thresholds (PT) in controls, interictal, preictal and postictal migraine.

Methods: Polysomnography and PT (to pressure, heat and cold) measurements were done in 34 healthy controls and 50 migraineurs. Subjective sleep quality was assessed by sleep diaries, Epworth sleepiness scale, Karolinska sleep questionnaire and Pittsburgh sleep quality index. Migraineurs who had their sleep registration more than 48 h from an attack were classified as interictal while those who were less than 48 h from an attack were classified as either preictal or postictal.

Results: Migraineurs reported more insomnia and other sleep-related symptoms than controls, but the objective sleep differences were smaller and we found no differences in daytime sleepiness. Interictal migraineurs had more awakenings (p=0.048), a strong tendency for more slow-wave sleep (p=0.050), lower thermal pain thresholds (TPT) (heat pain thresholds p=0.043 and cold pain thresholds p=0.031) than controls. Migraineurs in the preictal phase had shorter latency to sleep onset than controls (p=0.003). Slow-wave sleep correlated negatively with pressure PT and slow bursts correlated negatively with TPT.

Conclusion: Lower PT in interictal migraineurs seems related to increased sleep pressure. We hypothesize that migraineurs on the average suffer from a relative sleep deprivation and need more sleep than healthy controls. Lack of adequate rest might be an attack-precipitating- and hyperalgesia-inducing factor.

Keywords: Migraine phase, Sleep, Arousal, Pain thresholds

Background

Migraine and sleep are related, though the pathophysiological significance is unclear. Sleep problems are reported by many migraine patients [1]. Sleep related symptoms like tiredness and yawning are particularly frequent in the premonitory phase before an attack [2] while insufficient sleep may trigger a migraine attack [3]. There is also a growing body of neurophysiological evidence suggesting that CNS-excitability changes take place in the preictal state [4,5].

However, there are few polysomnographic (PSG) studies on migraine patients. For patients with sleep-related migraine it has been found that high-frequency arousals are reduced the night before a migraine attack compared to the interictal phase [6]. If disturbed sleep induces, or is related to the triggering of migraine attacks, decreased sleep quality should be consistently found in the preictal phase. If, on the other hand, the headache itself is the main cause for the disturbed sleep in migraine, we would expect decreased sleep quality to be found mainly in the postictal period. It should accordingly be useful so compare objective PSG sleep quality between interictal, preictal and postictal periods in migraine patients.

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The relationship between poor sleep quality and migraine pain is still incompletely understood. Reduced pain thresholds (PT) have been found during [7] and before [5] a migraine attack. Since sleep loss and REM sleep loss tend to induce increased pain sensitivity in healthy people [8], it can also be hypothesized that a disturbed sleep structure can cause the observed pre-attack hyperalgesia in migraineurs.

Since the association between subjective and objective sleep quality and the relationship between sleep, migraine cycle and pain physiology is incompletely known in migraine, we intended to study these relationships in a blinded and controlled study design. Our main aim was to compare subjective and objective sleep quality variables and PT in headache free controls and migraine patients in interictal phase. Secondly, we wanted to evaluate PSG sleep quality and PT in interictal, preictal and postictal phases. Thirdly, we intended to perform an explanatory correlation study to enlighten the association between sleep parameters and PT in controls and migraineurs in the three phases.

Methods

Participants

One-hundred and twenty six persons, 85 women and 41 men, (age range 18 to 64, mean age 38.9 years), participated in the study. 24 participants with tension type headache will be reported in another paper. They were mainly recruited by advertising in local newspapers for people between 18 and 65 years with- and without headache. Volunteers were examined by a headache specialist who diagnosed patients according to the ICDH-II criteria [9]. Subjects with two to six episodes per month of migraine (M), with- (MA) and without aura (MwoA) were selected. Based on the headache diary (see below), the sleep recordings were divided into interictal, preictal (48 h before the next attack), and postictal (within 48 h after the previous attack). A cutoff of 48 h was chosen to retain power in the interictal vs. control group comparisons, and because the vast majority of reliable premonitory symptoms do not occur until about 24 h before the attack [10]. Three migraine patients with midictal PSG, fulfilling both preictal and postictal criteria, were excluded from this analysis.

Subjects with coexisting frequent migraine and tension-type headache (TTH), other major health problems (sleep disease, hypertension, infection, neoplastic disease, neurological disease, CNS- implants, cardial- or pulmonary disease), chronic or acute pain, regular use of neuroleptic-, antiepileptic- or antidepressant drugs, analgesics, or drugs for migraine prophylaxis the last four weeks), or subjects who were pregnant, were not included. Painkillers or triptans for acute migraine were allowed.

Thirty-four headache-free controls and thirty-three migraine patients in interictal phase, nine in the preictal and eight in the postictal phase were available for analysis in the present study (Table 1). MA and MwoA patients were combined because few preictal and postictal patients were available.

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

Questionnaires and diaries

All participants filled in sleep and headache diaries two weeks before and two weeks after the sleep registration. From diaries, the average sleep-time (day and night), awakenings per night, and headache days were calculated. Individual averages were calculated for each subject. For each night sleep latency was (categorized as 0: <15 min, 1: 15–30 min, 2: 31–90 min, 3: > 90 min), long (≥30 min) and short (<30 min) and the average for 14 days was calculated. For sleep latency dichotomous variables (0: < 30 min, 1: ≥30 min) was also analyzed.

Every subject answered several questionnaires including Epworth sleepiness scale (ESS) [11], questions adapted from Karolinska sleep questionnaire (KSQ) [12], Pittsburgh sleep quality index (PSQI) [13] and Hospital anxiety and depression subscales (HADS) [14]. The nine PSQI questions (indicating the frequency of common sleep problems; 0–3) were summed into a combined global score variable (PSQIgs, possible range 0–27) [13]. "Bothersome tiredness" was categorized by as: none, less than 7 days per month, 7–14 days, > 14 days per month, daily (0–4). HADS depression and anxiety subscores, each based on seven of the 14 questions, were calculated. Every subject also quantified their usual pain intensity, the length of their usual headache attack, and scores for photophobia and phonophobia in addition to migraine history duration (Table 1).

PSG

Patients and controls underwent a full night ambulatory sleep study unattended in our patient-hotel. The hotel is very close and connected by an indoor walking bridge to our department. PSG was recorded by a Notta recorder (EEG Technology Int.bv, 6092 NM Leveroy, The Netherlands) and analyzed with Stellate Harmonie software (Stellate, Montreal, Quebec, Canada). Eight EEG electrodes were placed according to the International (10–20) system [15] (F3, F4, C3, C4, P3, P4, O1, O2 plus Pz reference and Cz ground); two electrooculografic electrodes (EOG) applied two cm laterally and, respectively, two cm above and below the right and left lateral eye cantus. EOG-reference electrodes were applied to the left (A1) and the right (A2) mastoids. Surface electromyography (EMG) was registered from the submental and left anterior tibial muscle.

Table 1 Background and headache-related data for participants in the present study: Counts or mean (SD)

	C (n=34)	INT (n=33)	PRE (n=9)	POST (n=8)
Age (years)	39.6 (13.7)	36.4 (12.9)	41.7 (11.3)	41.1 (11.2)
Sex: F, M	20, 14	25, 8	6, 3	7, 1
BMI (kg/m2)	25.3 (3.4)	23.5 (3.1)	26.2 (4.8)	24.1 (2.8)
Coffeinated beverages (cups per day)	4.0 (3.5)	2.3 (2.3)	4.2 (3.0)	3.8 (2.6)
Alcohol: 0 (never) to 5 (4 or more per week)	**2.9 (1.0)**	**2.2 (1.2)****	2.1 (1.2)	**1.8** (1.2)*
Nicotine: yes, no	6, 28	28, 5	6, 3	7, 1
Days since last menstruation	18.9 (8.6)	14.2 (7.6)	15.0 (13.9)	13.8 (10.1)
Married or common-law partner, single	25, 9	19, **14**	9, **0**$^{\#}$	7, 1
HAD depression score (0–21)[1]	1.6 (2.1)	2.5 (2.5)	2.1 (2.0)	2.1 (2.0)
HAD anxiety score (0–21)[1]	**2.9 (2.6)**	**5.7 (3.0)*****	**4.7 (2.7)***	6.1 (4.4)
MA, MwoA	na	9, 24	2,7	3, 5
Migraine time in diary (h/day)	na	1.4 (1.9)	1.5 (1.4)	2.1 (1.4)
Headache frequency (1–4)	na	2.2 (0.8)	2.2 (0.4)	2.3 (0.7)
Headache intensity (1–4)	na	2.6 (0.5)	2.2 (0.7)	2.5 (0.5)
Migraine duration (years)	na	20.0 (15.1)	24.2 (10.7)	23.3 (12.4)
Photophobia (0–2)	na	1.1 (0.3)	1.2 (0.7)	1.4 (0.5)
Phonophobia (0–2)	na	1.0 (0.5)	0.9 (0.8)	1.3 (0.7)

C: controls. *INT*: Interictal migraine, *PRE*: Preictal migraine. *POST*: Postictal migraine. *C-INT, INT-PRE and INT-POST* differences were all non-significant. *na*: not available. Mann–Whitney *U*-test): *p<0.05, **p<0.005 ***, p<0.001 (in comparison to controls) $^{\#}$ p<0.05 (in comparison to interictal group). [1]Sum of seven questions about depression and anxiety symptoms respectively during the last week from the Hospital Anxiety and Depression Scale questionnaire.
Significant differences are emphasized with bold types.

The following sensors were also applied for respiration and circulation measurements: a three-point oronasal airflow thermistor, a snore microphone, bands around thorax and abdomen to measure respiratory movements (Ultima Respiratory Effort Sensor™, piezo-electric crystals, Breabon Medical Corporation, Carp, Ontario, Canada), a body position sensor, (Ultima Body Position Sensor™, Breabon Medical Corporation, Carp, Ontario, Canada), an infrared index finger oximeter, and two ECG electrodes. The participants were instructed to go to bed, sleep as normal and write down lights-off and lights-on time from a synchronized watch.

Fifteen sleep recordings (seven controls, eight migraine patients) were excluded for technical reasons such as battery error or lost electrodes.

PSG data analysis

Analyses were done from noted time for "lights off" in the evening to "lights on" in the morning. Sleep stage percentages N1, N2, N3 (SWS="slow-wave sleep"), REM, arousals and respiratory events were visually scored. Automatic analysis was applied for leg movements. Sleep staging was performed according to "The AASM Manual for the scoring of sleep and associated events" from 2007 [16] with a few exceptions, as described below.

Fast and slow arousals were scored separately. First fast arousals were defined according to the AASM-manual [16] as an abrupt shift of EEG frequency (alpha, theta and/or faster than 16 Hz activity) lasting 3–30 s, separated with at least 10 s of sleep. Arousals were scored in NREM and in REM sleep if associated with increased EMG for more than one second. Although the upper limit for arousal definition is not defined by AASM, we chose to use 30 s in the present study to avoid ambiguous counts induced by random timing of sleep staging epochs. In this way, an e.g. 25-s EEG-frequency increase will always be counted as one arousal event regardless of its relationship to the epoch boundaries. Therefore, only change in EEG-activity containing dominating frequencies of 8 Hz or more lasting more than 30 s was classified as an awakening. If a sleep stage N2 K-complex was followed by a high frequency arousal, we scored the arousal without changing the sleep stage to N1. We also recorded two additional PSG measures of slow-wave arousal in NREM-sleep: Delta-bursts (D-bursts), defined as a sequence of delta waves lasting 2 s or more and exceeding the background amplitude with at least one third [17], and K-bursts, defined as at least two consecutive K-complexes [17]. A K-complex is a negative deflection followed by a positive component with a minimum duration of 0.5 s and minimum peak to peak amplitude of 75 μV observable in at least three EEG channels. Awakening-, arousal- K- and D-burst- indexes were calculated as event number per sleep hour. Since K- and D-bursts probably reflect similar physiological processes [18] they were combined into a KD-index in the present paper. Scoring of respiratory events was first done

automatically by the Stellate Harmonie software (Stellate, Montreal, Quebec, Canada). Manual sleep scoring, arousal scoring, and event editing was performed by the first author (specialist in clinical neurophysiology) assisted by a sleep expert (the last author).

Pain thresholds (PT)

Thermal PT and pressure PT (algometry) were recorded one hour before the participants had their PSG equipment mounted. Heat and cold PT (HPT and CPT) were measured separately in a fixed order on thenar and the medial forehead on both sides with methods of limits (MSA Thermotest, thermode area 25× 50 mm^2, Somedic Sales AB, Sweden). Temperature was increased by 1°C/s from a 32°C baseline to a 50°C maximum for three HPTs followed by three decreasing temperature stimuli to 5°C minimum for CPT. Pressure PT (PPT) were measured at four sites on both sides in a fixed order: m. temporalis (10 mm lateral to the external angle of the orbit), m. splenius (C2 level just at the edge of the trapezius muscle about 35–40 mm lateral to the midline), m. trapezius (10 mm lateral to the midpoint of a line connecting the acromion and the spinous process of C7) and over distal phalanx middle finger (Algometer type II, probe area 1 cm^2, Somedic Sales AB, Sweden). Pressure was increased with 30 kPa/s. Thresholds were repeated three times, left before right, and the average was calculated. All thresholds were measured by one out of two technicians. In subjects who did not feel cold pain at 5°C, we used the substitution value 4°C. Thermal PT were expressed as differences from baseline: HPTd (HPT-32) and CPTd (32-CPT) and averaged (right and left sides from all recorded sites) for the present analysis.

Blinding

Technicians and scorers of PSG and pain thresholds measurements were blinded for diagnoses. Two nurses administered the participant appointments and questionnaires. They also accompanied the participants to the technicians after having instructed the participant not to tell anything that could reveal their headache trait or state.

Statistics

Statistical analyses were performed with PASW statistics v.18 and SYSTAT version 11. Univariate two-group comparisons were made by nonparametric Mann–Whitney tests. Categorical data were analyzed with Pearson chi-square test or Fisher's exact test if any cross tab cells had expected count less than five. The primary univariate comparisons were 1) between controls and interictal migraine patients and 2) between interictal and preictal and between interictal and postictal subgroups. After square root transformation, age-adjusted partial correlation coefficients were calculated while four ANOVAS (PSQI, insomnia, tiredness and pain related sleep problems as dependent variables) were performed to check if the group difference between MIG and CO remained when adjusting for relevant confounders (anxiety, depression, PLM, and AHI). Post hoc Spearman's rho correlations were calculated between awakening index, stage N3 and fast arousals. Two-sided p-values less than 0.05 were regarded as significant.

The power in t-tests to detect large effect sizes equal to 1.0 SD in two-group comparisons between the interictal and preictal/postictal samples were 76% for INT-PRE and 72% for INT-POST. The power to detect medium effect sizes equal to 0.8 SD in the CO – INT two-group comparison was 91%.

Results

Migraineurs reported a higher HADS-anxiety score and consumed alcohol less frequently than controls. None of the patients in the preictal phase were single (Table 1).

Migraineurs reported significantly more subjective sleep problems. They had more insomnia symptoms, tiredness, global sleep problems (PSQI) and pain-related sleep difficulties compared to controls (Table 2). The difference remained significant in ANOVAs adjusting for relevant confounders (anxiety, depression, PLM, and AHI), for PSQI (p=0.004), insomnia (p=0.002), tiredness (p=0.018) and pain related sleep problems (p=0.02). In the sleep diary they reported significantly more long awakenings than controls while sleep times did not differ. Migraineurs reported longer sleep latency in the dichotomous pathological/non-pathological variable. However, there were no significant differences in sleepiness (daytime hypersomnia) as measured by ESS (Table 2).

A slightly higher awakening index and a strong tendency to more stage N3 sleep and less fast arousals were found in the INT group compared to controls (Table 3). Preictal migraineurs had shorter latency to sleep onset than interictal migraineurs. TPT were lower in interictal migraine compared to controls (Table 3).

Among controls and migraineurs there was a positive partial age-adjusted correlation between anxiety and superficial sleep (Table 4). In interictal migraineurs there was also a negative correlation between SWS and anxiety. Fast arousals correlated positively with insomnia (Table 4). The amount of SWS correlated negatively with PPT (Figure 1) and slow bursts correlated negatively with TPT. Among preictal migraineurs there was a negative correlation between HPT and sleep stage N1 (Figure 2) (p=0.025). In the postictal subgroup REM correlated negatively with CPT (r=−0.79, p=0.03).

Migraine history duration correlated (age adjusted) negatively with sleep stage N3 (r=−0.41, p<0.05), while a tendency also was observed for KD-bursts (r=−0.33,

Table 2 Sleep diary and sleep related symptom mean values (SD) in controls and all migraine patients

	C (n=34)	M (n=53)
Average diary sleep time (hour)	7.3 (0.8)	7.2 (1.0)
Long awakenings in diary (no)[1]	**0.10 (0.18)**	**0.25 (0.36)***
Short awakenings in diary (no)[2]	0.15 (0.24)	0.31 (0.50)
Sleep latency in diary[3,4]	0.40 (0.43)	0.56 (0.61)
Categorized sleep latency in diary (0 ≤ 30 min, 1 > 30 min)[4]	**32, 2**	**37,15#**
Epworth sleepiness scale (0–24)	5.6 (3.1)	6.5 (3.6)
Snoring/apnea KSQ score (0–8)	1.7 (1.6)	1.8 (1.7)
Daytime tiredness frequency (0–4)	**0.68 (0.84)**	**1.15 (0.95)****
Insomnia KSQ score (0–16)[5]	**3.4 (2.3)**	**6.1 (2.9)*****
PSQIgs (0–21)[6]	**3.8 (2.6)**	**6.3 (3.2)*****
Pain-related sleep trouble (1–4)[7]	**1.3 (0.7)**	**1.9 (1.0)****
Restless legs (0–1)[8]	0.1 (0.4)	0.3 (0.5)

[1]Awakenings lasting more than 30 min, [2]wakenings lasting less than 30 min. [3]Each day was categorized as 0: <15 min, 1: 15–30 min, 2: 30–90 min, 3: > 90 min and the individual mean was computed .[4] One sleep latency was not assessable and was excluded. [5]Sum of four insomnia-questions in KSQ (Karolinska sleep questionnaire), [6] Pittsburgh sleep quality index (PSQI) global score, [7] Frequency of pain-related sleep problems during the last month from the PSQI questionnaire, [7]RLS defined as a positive answer to all four obligatory symptom-criteria. # p=0.012, Fisher exact test.: *p<0.05, **p<0.005 ***, p<0.001, Mann–Whitney *U*-test (in comparison to controls).
Significant differences are emphasized with bold types.

p=0.067). We found no significant correlations between our sleep variables and headache frequency or headache intensity.

Post hoc we found a negative correlation in interictal migraineurs between N3 sleep and awakening index (rho=−0.45, p=0.009) and fast arousals (rho=−0.56, p=0.01) (not tabulated).

Discussion

The main findings in this blinded controlled study were that migraineurs reported more sleep related symptoms than controls while the corresponding differences in sleep diaries and PSG sleep quality variables were much smaller. Interestingly, migraineurs had lower PT and a strong tendency to more N3 sleep. We hypothesize that the latter

Table 3 PSG sleep quality and arousal mean values (SD) and pain thresholds for controls and phase-related migraine subgroups

	C (n=34)	INT (n=33)	PRE (n=9)	POST (n=8)	C vs INT differences	Phase differences
Total sleep time (min)	409 (68)	435 (61)	440 (62)	445 (53)		
Sleep efficiency (%)	90 (08)	91 (6)	91 (6)	94 (3)		
Latency to sleep onset (min)	12.8 (14.6)	**10.3 (17.8)**	**2.0 (3.7)**	6.5 (7.9)		INT>PRE**
Awakening index (no/h)	**1.0 (0.6)**	**1.3 (0.7)**	1.2 (0.7)	0.8 (0.6)	INT>C*	
Wake after sleep onset (min)	31 (27)	32 (18)	41 (23)	22 (14)		
Stage 1 (min)	27 (19)	32 (15)	41 (16)	33 (27)		
Stage 2 (min)	197 (47)	201 (44)	198 (46)	195 (77)		
Stage 3 (min)	**86 (31)**	**97 (28)**	99 (35)	108 (41)	INT>C(*)	
REM (min)	99 (26)	106 (35)	102 (36)	108 (28)		
Apnea-hypopnea index (per hour)	2.7 (3.3)	2.4 (3.0)	4.3 (4.9)	0.9 (0.8)		
Fast arousal index (per sleep hour)	**18.3 (5.7)**	**16.3 (9.1)**	13.4 (5.9)	12.3 (5.5)	C>INT(*)	
D-burst index (per sleep hour)	11.8 (8.0)	9.5 (7.5)	10.1 (8.4)	13.9 (9.1)		
K-burst index (per sleep hour)	3.0 (3.8)	3.3 (2.5)	1.9 (1.2)	3.4 (3.2)		
Slow arousal index (per sleep hour) [3]	14.8 (10.9)	12.9 (9.1)	12.0 (8.6)	17.3 (11.9)		
PPTavg[1] (kPa)	661 (249)	549 (135)	582 (194)	539 (70)		
HPTavg[2] (°C)	**13.4 (3.1)**	**11.7 (3.6)**	13.1 (2.3)	13.6 (2.6)	INT<C*	
CPTavg[2] (°C)	**20.8 (6.3)**	**17.2 (6.9)**	19.5 (5.8)	18.4 (6.3)	INT<C*	

C: controls. *INT*: Interictal migraine, *PRE*: Preictal migraine. *POST*: Postictal migraine. Significant differences (*) p=0.05, *p<0.05, **p<0.005 (Mann–Whitney *U*-test). avg: Regional averages from either [1]splenius, trapezius, temporalis, and index finger (pressure pain thresholds, PPT) or [2]forehead and palm (heat and cold pain thresholds, HPT and CPT, expressed as differences from the 32°C baseline) registered after noon before sleep. [3] The sum of K- and D-burts.
Significant differences are emphasized with bold types.

Table 4 Age-adjusted partial correlations between objective sleep and sleep quality, anxiety and pain thresholds in healthy controls and interictal migraineurs

Objective sleep	Subjective symptoms			Pain thresholds		
Controls n=34	Insomnia	PSQIgs	Anxiety	PPT	HPT	CPT
N1 min	0.28	0.15	**0.43***	−0.33	−0.12	−0.04
N2 min	−0.12	−0.17	−0.09	−0.20	0.21	0.13
N3 min	−0.27	−0.28	−0.11	0.06	−0.18	−0.13
REM minutes	−0.01	−0.09	0.20	−0.02	−0.14	−0.11
Fast arousals per sleep hour	−0.05	0.12	−0.09	−0.06	0.32	0.31
Slow arousals per sleep hour	−0.06	0.15	−0.31	−0.22	−0.05	−0.08
Interictal						
migraineurs, n=33						
N1 min	0.25	0.35	**0.45***	0.15	−0.01	0.14
N2 min	−0.04	0.16	**0.43***	0.27	0.05	0.08
N3 min	−0.01	−0.20	**−0.37***	**−0.37***	−0.23	−0.34
REM minutes	0.12	−0.08	−0.17	0.01	0.21	0.07
Fast arousals per sleep hour	**0.43***	0.32	0.16	0.05	−0.18	−0.16
Slow arousals per sleep hour	0.01	−0.15	−0.05	0.06	**−0.39***	**−0.41***

P*<0.05, P**<0.01.

Significant differences are emphasized with bold types. *p<0.05.

findings are explained by an increased sleep pressure in the interictal phase.

Subjective and objective sleep quality in controls and interictal migraineurs

In accordance with other studies migraineurs presently report more subjective symptoms of anxiety [19], insomnia [20] and subjective tiredness [21], than healthy subjects. However, in contrast to these clear differences in subjective symptoms the differences in objective sleep diary variables, daytime hypersomnia scales, and PSG sleep parameters between migraineurs and controls were smaller. A similar discrepancy has previously been found among chronic insomniacs [22]. Insomnia is also a risk factor for migraine [23]. Although patients with known and previously diagnosed sleep disorders were excluded from the present study we can hardly rule out that some migraineurs had an undetected insomnia. Indeed, the high PSQI suggest that some migraine patients may suffer from a sleep disorder. However, PSQI is a summary measure that incorporates insomnia, hypersomnia, snoring and other symptoms and can not be interpreted as a specific sign of insomnia alone. In this study we have focused on sleep differences between our groups, not individualized sleep diagnoses. Furthermore, we excluded those with a clear history of comorbid sleep disorders to characterize the migraine-related sleep dysfunction (including insomnia).

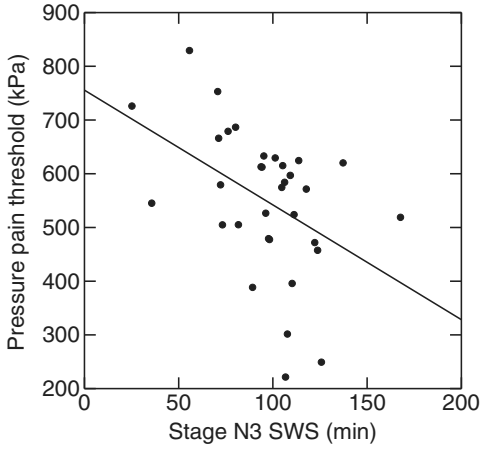

Figure 1 Pressure pain thresholds and amount of slow wave sleep (SWS) in interictal migraine. Less N3 sleep is associated with high pressure pain thresholds (age-adjusted r= −0.38, p<0.05).

The more objective findings were somewhat inconclusive for insomnia as more migraineurs reported long sleep latencies and long awakenings while PSG sleep latency and total sleep times in both PSG and sleep diaries did not differ from controls.

Despite excessive daytime tiredness among migraineurs we found sleepiness (ESS) to be normal, in agreement with Seidel et al. [24]. However, slightly elevated ESS abnormality rates (ESS cutoff ≥10) in migraine have been observed in a larger population study [1], suggesting that migraine patients on the average achieve somewhat less sleep during nighttime than they actually need.

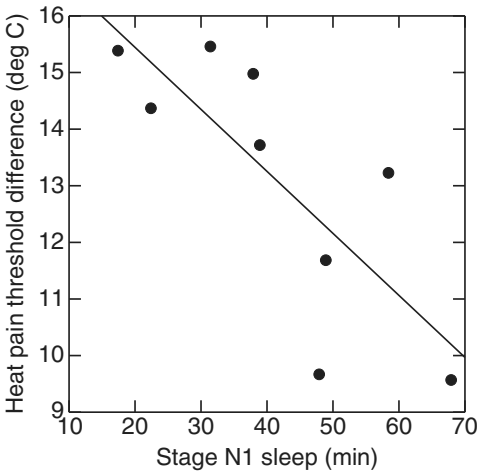

Figure 2 Preictal migraine subgroup. High levels of superficial stage N1 sleep is associated with relative heat-pain hyperalgesia (age-adjusted r=−0.80, p=0.02).

In the present study both controls and patients with interictal migraineurs had increasing amount of N1 sleep with increasing symptoms of anxiety. However, in the migraine group we also found increasing symptoms of insomnia and decreasing subjective sleep quality with increasing amount of fast arousals. We also found decreasing amount of SWS with increasing amount of anxiety in the interictal migraine group. Hence sleep quality seems to be more vulnerable (i.e. disturbed by anxiety or subjective insomnia) among migraineurs than healthy controls.

In PSG recordings we found almost significant (p=0.05), tendencies towards less fast arousals and more N3 sleep among migraineurs in the interictal phase than among controls. Because fast arousals occur more frequently in superficial than deep NREM sleep [25] it is possible that less fast arousals partly is a passive reflection of more N3 sleep. More deep sleep is one factor that usually indicates better sleep quality [26], but in migraineurs it was paradoxically accompanied by more awakenings. It is possible that awakenings increase sleep pressure and induce compensatory more deep sleep between awakenings. On the other hand, it seems illogic that nights with more awakenings is the explanation for more deep sleep because negative correlations were found between N3 sleep and both awakening index and fast arousals. Another explanation for the paradoxical findings could be subgroup differences. Our findings are only partly in line with findings of Karthik et al. [27]. In that study thirty migraineurs without aura, recruited from a tertiary university hospital, were found to have longer latency to sleep onset, less NREM sleep, lower arousal-index, more awakenings, longer time in bed and more awake time compared to 32 controls. In PSG, we did not find longer latency to sleep onset or less NREM sleep among migraineurs, but we have included migraineurs from advertisement and not hospital patients. Furthermore, Karthik et al. [27] did not say anything about blinding or the temporal relation to the attack.

De Gennaro et al. [28] found reduced amount of fast arousals and increased SWS the night after sleep deprivation. Hence, our PSG findings could indicate sleep deprivation among the interictal migraineurs. However, according to the sleep diaries, sleep deprivation was probably not present in this study, unless one postulates too low power to detect small differences for sleep time in diaries or that migraineurs need more sleep than controls. Even though more SWS is found after sleep deprivation, Sforza et al. [29] did not find more slow bursts while Nicholas et al. [30] found increased numbers of K-complexes per minute in sleep stage 2 after sleep deprivation. 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 [31]. These findings have been interpreted as hypofunction of the arousal system [31], but we suggest that this may be related to a relative sleep deprivation and that migraineurs are relatively sleep deprived and need more sleep than healthy controls.

Differences in objective sleep among migraineurs in inter, pre and post ictal phases

A shorter latency to sleep onset in the preictal phase compared to interictal phase was the only significant phase difference in PSG variables we found among migraineurs. As far as we know, reduced sleep latency in the preictal phase has not been described before. Hence, preictal migraineurs seem to have greater sleep pressure that fits with premonitory symptoms reported in the preictal phase [10] and daytime EEG changes in the preictal phase [4]. We found no other significant differences in our PSG measures between migraineurs in different phases, probably due to too low power, because we captured only 9 patients in the preictal and 8 in the postictal phase.

Less arousals [6] and more SWS (and also REM sleep) [32] have been found during the night before an attack. We could not confirm these findings in our study. Göder et al. [6] and Dexter [32] included patients with morning- or sleep- related migraine attacks and compared intra individually nights before an attack with nights without ensuing attacks in order to improve the statistical power of their studies. In contrast we compared subgroups inter individually and we also included those with sleep recordings between 24 and 48 h before attack. Because only

one of our nine preictal patients had attacks usually initiated by sleep, the study populations are not quite comparable, possibly explaining the discrepant results. As we did not find changes in sleep quality in the postictal group, our result do not suggest that the polysomnographic changes are caused by the attack or sleep disturbances that may accompany the attack in some patients.

Pain and sleep

We found decreased PT in the interictal migraine group 48 h from any attacks in accordance with Schwedt et al. [33]. However, the latter studies did not exclude preictal migraine from their "interictal" groups. Previously, we did not find significant thermal PT differences between interictal migraine and controls, neither with 24 nor 72 h cut-offs [5], possibly caused by lack of power. The same study showed decreased pain thresholds 24 h before the attack [5] compared to the interictal period. However, the present study was not designed to re-address the latter question as longitudinal observations were not included. Allodynia during a migraine attack has also been described previously [34].

As slow bursts are frequent before and during slow wave sleep, especially in the first sleep cycles [35], these slow bursts are possibly related to sleep pressure or sleep need. Then, both increased N3 sleep and more slow arousals in a stable interictal phase could be assumed to be measures of increased sleep pressure. N3 sleep correlated negatively with PPT and slow burst correlated negatively with TPT in the present study, hence signs of increased sleep pressure seems to be associated with lower pain thresholds. The relationship between PSG signs of a tired (or "weary") brain and PT does not seem unreasonable as increased pain sensitivity has been found among healthy volunteers after sleep deprivation [8]. Lovati et al. [36] also found in a questionnaire study that migraineurs with head allodynia during attack reported more symptoms of insomnia.

Apparently it seems inconsistent that HPT in the preictal migraine group was negatively correlated to superficial sleep, that is N1 (Figure 2), and not to N3 as in the interictal phase. The reason is unclear, but is should be noted that, compared to controls, interictal migraineurs both had increased SWS and reduced PT. As explained above, we apprehend increased SWS as a probable compensation for increased sleep pressure. Hence N3 could be a measure of both foregoing cerebral tiredness and the ability to compensate for it. As the needs accumulate, in our study indicated by preictally reduced latency to sleep onset in PSG, lack of compensation might induce, or contribute to a migraine attack. When maximum N3 sleep is achieved, any further need for repose could be reflected by the less restful N1 sleep.

Migraine and sleep

With respect to a hypothesized relative sleep deprivation it makes sense that migraineurs have increased symptoms of tiredness, have either normal EEGs or subtle findings that may reflect drowsiness [37], and tend to have low PT. Even though small undetected differences can not be ruled out, sleep diaries revealed normal sleep times among migraineurs. But why should migraineurs need more rest than controls and how should lack of sleep initiate a migraine attack? More deep sleep may possibly be induced either by increased awake neuronal activity [38] or an absolute sleep deprivation [28]. Since the latter option apparently is not the case here (although a relative deprivation can be operative), increased neural activity might be the link between mental stress (both as state and trait factors (i.e. anxiety symptoms)) and the onset of a migraine attack [39]. Partial correlation adjusted for age indicates that migraineurs have reduced SWS with increasing headache duration. If amount of SWS goes down to a "normal level" with increasing duration of the migraine, this might be a parallel phenomena to reduced migraine attack prevalence after menopause [40].

Strengths and limitations

The strengths of this study are the blinded, controlled, and prospective design. The participants were mainly recruited by advertising in local newspapers, in contrast to a hospital-based migraine population which may include more severe and longstanding cases. A study design with repeated PSGs may be more powerful for the detection of phase-related differences. In addition, a so-called first-night effect should be considered [41]. Even though a first-night effect has been shown to occur in inpatient PSGs, there are also findings indicating reverse first night effect for some subjects (i.e., increased sleep quality) [42]. Even with two PSGs it is not possible to eliminate the first-night-like effects, because these might last more for than one night in some subjects [41]. In addition, a single PSG design may also have some advantages because serial PSGs can be affected by individually variable order-effects [43]. A slight underestimation of sleep problems, as compared to the general migraine population, is expected in our study because patients with any known and diagnosed previous sleep disorders were excluded, however, this exclusion is a strength regarding the major aims of the study. This study was exploratory and we did not adjust for multiple comparisons because we did not want to increase type II failures on the cost of reducing type I failures [44,45]. Another limitation is the rather low power for comparing interictal, pre- and postictal subgroups and the possibility of both type I and type II errors is acknowledged. Independent replication of our results is accordingly needed.

Conclusion

In conclusion, migraineurs reported more sleep related symptoms than controls, but the differences in sleep diaries and PSG between the groups were smaller. Migraineurs in the interictal phase had lower PT and tended to have more SWS than controls. Pain sensitivity seems related to increased sleep pressure among interictal migraineurs. Preictal migraineurs also seem to have an increasing sleep pressure. We hypothesize that migraineurs on the average might suffer from a relative sleep deprivation and need more sleep than healthy controls. Lack of adequate rest might be an attack-precipitating- and hyperalgesia-inducing factor. To our knowledge the relationship between sleep and pain has not been investigated in migraineurs before in a blinded, controlled design. For this reason and due to the small number of subjects in the subgroups, the present results should be considered as preliminary and studied further in a longitudinal design.

Competing interest

The authors declare that they have no competing interests.

Authors' contribution

ME mounted some PSGs and performed some pain threshold measurements, analyzed all PSGs, performed the statistical analysis, prepared the initial draft and was the main author of the present manuscript. KH and LJS included patients in the study. GG was contact person for the participants, handled and typed the questionnaires. MS mounted most of the PSGs and performed most of the pain threshold measurements. TS had the original idea of the study; he has made all the data files for statistics and been the main supervisor in all processes. All authors have contributed to the practical plans for the study, read, revised and approved the final manuscript.

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Sleep-related and non-sleep-related migraine: interictal sleep quality, arousals and pain thresholds

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Abstract

Background: The mechanisms associating sleep and migraine are unknown. No previous polysomnographic (PSG) or pain-threshold (PT) study has compared patients with sleep-related migraine attacks (SM), non-sleep related migraine attacks (NSM) and healthy controls.

Methods: We have performed a blinded, prospective exploratory study with case–control design. Thirty-four healthy controls, 15 patients with SM and 18 patients with NSM had interictal PSG heat-, cold- and pressure PT (HPT, CPT, PPT) recordings and completed diary- and questionnaire on sleep and headache related aspects.

Results: NSM patients had more slow-wave sleep (SWS) and more K-bursts than SM patients (K-bursts: $p = 0.023$ and SWS: $p = 0.030$) and controls (K-bursts: $p = 0.009$ and SWS: 0.041). NSM patients also had lower HPT and CPT than controls ($p = 0.026$ and $p = 0.021$). In addition, SM patients had more awakenings and less D-bursts than controls ($p = 0.025$ and $p = 0.041$).

Conclusion: SM- and NSM patients differed in objective-, but not subjective sleep quality. NSM patients had PSG findings indicating foregoing sleep deprivation. As foregoing sleep times were normal, a *relative* sleep deficit might explain reduced PT among NSM patients. The SM patients had signs of slightly disturbed sleep.

Keywords: Sleep; Arousal; Migraine; Sleep-related migraine; Non-sleep related migraine; Subjective sleep quality; Polysomnography; Pain thresholds

Background

Approximately on third (24-42%) of migraine patients have attacks almost exclusively related to sleep or awakening (sleep migraine = SM) [1,2]. According to ICHD-II SM is not a separate migraine subtype [3], but sleep-related symptoms are among the most frequently cited trigger factors [4,5]. Sleep-related *headache* is defined by American Academy of Sleep Medicine (AASM) as complaints of headache (either migraine or other types) during sleep or upon awakening [6]. Sleep-related headache may also suggest the presence of an underlying sleep disorder [7,8].

Sleep disturbances are commonly reported by migraineurs [2,9,10]. However, it is not really known whether migraine attacks are the major cause of the reported sleep disturbances, whether coexistent sleep disturbances trigger migraine attacks during the night or if there are parallel (but non-causal) intrinsic pathophysiological mechanisms linking migraine and sleep problems [11,12]. One critical review article suggested that the significance of sleep as a migraine trigger still has not been conclusively determined [13]. Polysomnographic studies have been performed to detect sleep disorders and sleep characteristics in relation to migraine [14-16]; but the results are ambiguous. However, no previous study has compared sleep quality in patients with SM to patients with mainly non-sleep-related migraine attacks (non-sleep-related migraine = NSM). This comparison might clarify if disturbed sleep is a factor related specifically to nightly migraine attacks.

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Furthermore, the relationship between pain mechanisms and sleep might contribute to explain why some people wake up with migraine. A relationship between sleep and pain has previously been found as sleep loss decrease pain thresholds (PT) in healthy people [17-20]. Disturbed sleep also seems to reduce the descending inhibitory pain control system (DNIC) activity and thereby increasing somatic spontaneous symptoms [21]. Decreased thermal PT (TPT) have also been found 24 hours before migraine attacks [22]. Hence we hypothesized that polysomnographic (PSG)-measures of sleep quality, nightly arousals and PT would be changed among SM patients compared to NSM patients and healthy controls.

Our primary aim of this exploratory, prospective case–control study was to compare subjective and objective sleep quality, arousal indices and PT between SM- and NSM patients. The second aim was to compare sleep and pain variables between healthy controls (C) and SM- and NSM patients respectively. Thirdly, we wanted to explore the correlation between subjective and objective sleep, PT, and headache severity variables.

Methods

Participants

Sixty-one migraine patients (M) with and without aura were recruited by advertising in local newspapers. Volunteers called a nurse trained in headache research for a screening interview followed by a consultation with a headache specialist who verified the diagnosis according to ICDH-II [3]. Subjects with two to six migraine attacks per month were selected for the present study. Subjects with coexisting frequent migraine and tension-type headache (TTH), other major health problems (including regular use of neuroleptic-, antiepileptic- or antidepressant drugs, analgesics, or drugs for migraine prophylaxis the last four weeks), or subjects who were pregnant, were not included. Painkillers or triptans for acute migraine were allowed. Based on the headache diary interictal (>two days from attack), patients were selected for the present study and the methodological details have been published previously [23].

The migraineurs were divided in two subgroups according to when the headache *usually started.* Migraineurs answering either "upon awakening" or "during the night (waking me up)" were defined as having SM, whereas those who answered "during daytime before noon", "during daytime after noon" or "no regular onset time" were defined as having NSM. The pre- and postictal group were too small to qualify for a subgroup analysis. Thirty-three interictal migraineurs SM (n = 15) and NSM (n = 18) and thirty-four comparable controls according to age and sex were available for the analysis (Table 1). The study was approved by the regional ethics committee and participants signed an informed consent before inclusion.

Table 1 Baseline chracteristics and headache-related data: counts or mean (SD)

	C (n = 34)	*SM[1] (n = 15)*	*NSM[1] (n = 18)*
Age (years)	39.6 (13.7)	39.4 (14.3)	33.9 (11.4)
Sex: F/M	20/14	10/5	15/3
BMI (kg/m2)	**25.3 (3.4)**	23.6 (2.8)	**23.4 (3.4)** [3]
Caffeine beverages (cups per day)	**4.0 (3.5)**	2.7 (2.2)	**1.9 (2.4)** [4]
Alcohol: 0 (never) to 5 (4 or more per week)	**2.9 (1.0)**	2.3 (1.4)	**2.1 (1.1)** [4]
Nicotine: yes/no	6/28	2/13	3/15
Physical activity[2]	1.8 (1.2)	1.6 (0.9)	2.1 (1.4)
Days since last menstruation	18.9 (8.6)	16.0 (7.4)	13.3 (7.9)
Oral contraceptives: yes/no	7/13	5/5	5/10
Married or common-law partner/single	25/9	7/8	12/6
MA/MwoA		10/5	14/4
Headache time in diary (h/day)		1.7 (1.5)	2.0 (2.3)
Migraine time in diary (h/day)		0.8 (1.0)	1.8 (2.3)
Triptan days (0–14)		1.9 (2.3)	1.5 (2.4)
Analgesic days (0–14)		1.1 (1.6)	1.9 (2.3)
Headache days last 3 months		7.6 (7.6)	6.3 (3.3)
Headache intensity (1–4)		2.7 (0.5)	2.6 (0.5)
Migraine duration (years)		24.3 (17.7)	16.5 (12.0)
Photophobia (0–2)		1.1 (0.4)	1.1 (0.3)
Phonophobia (0–2)		0.9 (0.6)	1.1 (0.4)

Controls (C), SM: Sleep-related migraine attack group, and NSM: none-sleep-related migraine attack group.
[1]SM and NSM are the corresponding interictal subgroups (background data for interictal PSG and pain threshold variables reported in Table 3).
[2](0: seldom), 1:1-2x/week, 2:3x/week; sum of exercise and walking to workplace scores.
[3] NSM or SM ≠ C ($p < 0.05$). [4]NSM or SM ≠ C ($p < 0.01$).
Pearson chi-square test, Fisher exact test or Mann–Whitney U-test.
Significant differences are emphasized with bold types.

Questionnaires and diaries

Headache hours per day, average sleep time, sleep latency, long (≥30 min) and short (<30 min) awakenings per night were calculated and analyzed from sleep diaries for the 14 days preceding the PSG.

Epworth sleepiness scale (ESS) [24,25], questions adapted from Karolinska sleep questionnaire (KSQ) [26], Pittsburgh sleep quality index (PSQI) [27] and Hospital anxiety and depression subscales (HADS) [28] were administered. The seven PSQI questions (indicating the frequency of common sleep problems; 0–3) were summed into a combined global score variable (PSQIgs, possible range 0–21) [27]. Bothersome tiredness was categorized (0–4) as "none", "less than 7 days per month", "7-14 days", "> 14 days per month" and "daily". We also had four questions concerning restless legs ("Urge to move the legs", "Rest worsens the urge", "Symptoms improve

with movement", "Symptoms worsen in the evening or night" [29]). Usual headache intensity, attack length, photophobia, phonophobia and migraine history duration were recorded from semi-structured nurse interviews (Table 1).

PSG

Patients and controls underwent a full night sleep registration with ambulatory equipment. They slept unattended in our patient-hotel in the neighbor building. PSG was recorded by a Notta recorder (EEG Technology Int.bv, 6092 NM Leveroy, The Netherlands) and analyzed with Stellate Harmonie software (Stellate, Montreal, Quebec, Canada). Eight EEG electrodes were placed according to the International (10–20) system [30] (F3, F4, C3, C4, P3, P4, O1, O2 plus Pz reference and Cz ground); two electrooculographic electrodes (EOG) applied two cm lateral and respectively two cm up and two cm down from the right and left lateral eye cantus. EOG-reference electrodes were applied to the left (A1) and the right (A2) mastoids. Surface electromyography was registered from submentalis muscles, the left anterior tibialis muscle and trapezius muscle bilaterally.

The following sensors from Breabon Medical Corporation, Ontario, Canada were applied for respiration and circulation measurements: a three-point oronasal airflow thermistor (Airflow temperature sensor R-510), bands around thorax and abdomen to measure respiratory movements (Ultima Respiratory Effort Sensor™, piezoelectric crystals) and a body position sensor (Ultima Body Position Sensor™). An infrared index finger oxymeter (model 8000 J3, Nonin Medical Inc, Plymouth, USA) and 10 mm silver chloride cup ECG electrodes (Natus Medical Inc, San Carlos, USA) were also used. The participants were instructed to go to bed as usual, and write down light-off and light-on times using a synchronized wrist watch.

PSG data analysis

Analyses were done from noted time for "lights off" in the evening to "lights on" in the morning. Respiratory events were scored automatically and edited visually later. The AASM manual suggest 2 hypopnea definitions based on nasal pressure signals but we had a thermistor. Therefore we chose to analyze hypopneas according to a modified "Chicago criteria" [31] (≥50% amplitude reduction or lower amplitude reduction in thermistor signals associated with 4% desaturation). Automatic periodic leg movement (PLM) analysis was implemented according to the AASM criteria [32]. Manual sleep scoring, arousal scoring and event editing were performed by the first author (specialist in clinical neurophysiology assisted by a sleep expert (last author)). Sleep staging was performed according to "The AASM Manual for the scoring of sleep and associated events" from 2007 [32] with a few exceptions, as described below.

In the present study we wanted to explore fast arousals besides slow arousals as separate events without considering the time interval between the different episodes. Since low frequency episodes have been defined and scored separately as arousals before [33], these D- and K-burst events were used as the "slow counterpart" to the fast AASM-arousals.

First, fast arousals were defined according to the AASM-manual [32] as an abrupt shift of EEG frequency (alpha, theta and/or faster than 16 Hz activity) lasting 3–30 seconds, separated with at least 10 seconds of sleep. Arousals were scored in NREM and in REM sleep if associated with increased EMG for more than one second. Although the upper limit for arousal definition is not defined by AASM, we chose to use 30 s in the present study to avoid ambiguous counts induced by random timing of sleep staging epochs. In this way, an e.g. 25-second EEG-frequency increase will always be counted as one arousal event regardless of its relationship to the epoch boundaries. Therefore, only changes in EEG-activity containing dominating frequencies of 8 Hz or more lasting more than 30 seconds were classified as an awakening. If a sleep stage N2 K-complex was followed by a high frequency arousal, we scored the arousal without changing the sleep stage to N1.

Secondly, we also scored two additional PSG measures of slow-wave arousal: Delta-bursts (D-bursts), defined as a sequence of delta waves lasting 2 s or more and exceeding the background amplitude with at least one third [33], and K-bursts, defined as at least two consecutive K-complexes [33]. A K-complex is a negative deflection followed by a positive component with a minimum duration of 0.5 seconds and minimum peak to peak amplitude of 75 μV. Both fast and slow arousals were scored when observable in at least three out of eight EEG channels. Awakening-, arousal- K- and D-burst- indexes were calculated as event number per sleep hour. Since K- and D-bursts probably reflect similar physiological processes [34,35] they were combined into a KD-index (resembling Cyclic Alternating Pattern (CAP) A1 phase) for correlation analyses in the present paper. The combined KD-index was also chosen rather than the individual K- and D-burst indexes to reduce the amount of analyses.

Pain thresholds (PT)

Thermal PT (TPT) and pressure PT (PPT) (algometry) were recorded one hour before the participants had their PSG equipment mounted. Heat and cold PT (HPT and CPT) were measured separately in a fixed order on thenar and the medial forehead on both sides with methods of limits (Senselab – thermotest, thermode area 25× 50 mm^2,

Somedic Sales AB, Sweden). Temperature was increased by 1°C/s from a 32°C baseline to a 50°C maximum for three HPTs followed by three decreasing temperature stimuli to 5°C minimum for CPT. PPT were measured at four sites on both sides in a fixed order: m. temporalis (10 mm lateral to the external angle of the orbit), m. splenius (C2 level just at the edge of the trapezius muscle about 35–40 mm lateral to the midline), m. trapezius (10 mm lateral to the midpoint of a line connecting the acromion and the spinous process of C7) and over distal phalanx middle finger (Algometer type II, probe area 1 cm^2, Somedic Sales AB, Sweden). Pressure was increased with 30 kPa/s. Thresholds were repeated three times, left before right, and the average was calculated. All thresholds were measured by one out of two technicians. In subjects who did not feel cold pain at 5°C, we used the substitution value 4°C. TPT were expressed as differences from baseline: HPTd (HPT-32) and CPTd (32-CPT) and averaged (right and left sides from all recorded sites) for the present analysis.

Blinding

For the PSG and PT measurements the technicians were blinded for diagnoses. Scoring of the PSG data was also performed blinded for diagnoses. Two nurses administered the participant appointments and questionnaires. They also accompanied the participants to the technicians after having instructed the participant not to tell anything that could reveal their headache trait or state.

Statistics

Statistical analyses were performed with PASW statistics v.18 and SYSTAT version 11. Since we found no significant differences in sleep-variables between migraine with and without aura, migraine patients were analyzed as one combined group in the present study.

Two-group comparisons were made by nonparametric Mann–Whitney tests. Categorical data were analyzed with Pearson chi-square test or Fisher's exact test if any cross tabular cells had expected count less than five.

Two-sided p-values less than 0.05 were regarded as significant. No adjustments for multiple comparisons were done because the study was exploratory and we wanted to avoid excessive type II errors and to avoid inappropriately testing of a less relevant universal null-hypothesis [36].

Partial correlation coefficients (adjusted for age) were calculated to explore the association between migraine severity, PT, sleep quality, arousal and sleep symptoms in SM- and NSM patients. Variables were square-root transformed before this calculation.

The power (based on Student's t-tests) to detect large effect sizes equal to 0.8 (and 0.9) SD in two-group comparisons were 78% (87%) for C - NSM, 73% (83%) for C – SM and 63% (73%) for SM – NSM.

Results

Baseline characteristics and headache-related data

There were no differences between SM- and NSM patients in baseline characteristics or headache data (Table 1). NSM patients had lower BMI and consumed less caffeine and alcohol than controls, and both NSM- and SM patients had more anxiety symptoms than controls. Triptans were taken within 48 hours before the interictal PSG by two SM- and three NSM patients.

Sleep related symptoms

Self-reported sleep related symptoms were not significantly different between SM- and NSM patients (Table 2). Both migraine groups reported more subjective sleep problems regarding insomnia, global sleep problems (PSQI) and pain-related sleep difficulties compared to controls. NSM patients were also more often subjectively tired than controls. However, there were no significant differences in hypersomnia as measured by ESS.

Polysomnographic sleep quality, arousals and PT

NSM patients had more slow wave sleep (SWS, stage N3, $p = 0.023$), more K-bursts ($p = 0.030$) and slightly higher nightly mean SaO2 than SM patients (Table 3). A slightly higher awakening index ($p = 0.025$), lower D-index ($p = 0.04$) and a tendency to more superficial stage N1 sleep were found among the SM patients compared to controls ($p = 0.05$). Fast arousal index among the SM patients did not differ from controls either judged by the whole night or separated into specific NREM or REM indexes (not tabulated). There were no significant differences in sleep efficiency, sleep-onset latency, or REM latency.

NSM patients spent more time in bed ($p = 0.041$), had more stage N3 slow-wave sleep ($p = 0.009$) and a lower index of fast arousals ($p = 0.041$) than controls. TPT were lower among the NSM patients than controls ($p = 0.026$ and $p = 0.041$). PPT also tended to be lower among the NSM patients compared to the SM patients ($p = 0.08$).

Partial correlations controlled for age in NSM and SM and controls

Among NSM patients the amount of sleep stage N1 correlated positively with headache frequency (Table 4). The amount of N3 sleep correlated negatively with PPT (Table 4, Figure 1). The amount of KD-bursts correlated negatively with TPT (Figure 2) and headache frequency (Table 4). Among SM patients, the KD-index tended to correlate positively with PPT. The amount of N2 sleep correlated negatively with insomnia and positively with PPT. The amount of sleep stage N3 correlated negatively with headache history duration. Among controls we found no significant correlations in objective versus subjective quality scores or versus PT (not tabulated).

Table 2 Sleep diary, sleep disorder symptoms, autonomic instability symptoms and emotional state

	C (n = 34)	SM (n = 15)	NSM (n = 18/17[10])
Average diary sleep time (hour)	7.3 (0.8)	7.2 (1.0)	7.3 (0.9)
Long awakenings in diary[1] (no)	0.1 (0.2)	0.2 (0.2)	0.3 (0.5)
Short awakenings in diary[2] (no)	0.2 (0.2)	0.2 (0.5)	0.3 (0.5)
Sleep latency in diary[3]	0.4 (0.4)	0.7 (0.8)	0.5 (0.5)
Epworth sleepiness scale (0–24)	5.6 (3.1)	5.5 (3.3)	7.2 (4.7)
Snoring/apnea KSQ score (0–8)	1.7 (1.6)	1.5 (1.3)	1.6 (1.8)
Daytime tiredness frequency (0–4)	**0.7 (0.8)**	1.1 (1.0)	**1.3 (1.0)** [12]
Insomnia KSQ score (0–16)[4]	**3.4 (2.3)**	**6.3 (3.7)** [12]	**5.8 (2.8)** [12]
PSQIgs (0–21)[5]	**3.8 (2.6)**	**6.5 (3.1)** [12]	**5.9 (3.5)** [11]
Pain-related sleep trouble (1–4)[6]	**1.3 (0.7)**	**1.8 (1.0)** [11]	**2.0 (1.1)** [12]
Restless legs (0–1)[7]	0.1 (0.4)	0.3 (0.5)	0.3 (0.5)
Depression score (0–21)[8]	1.6 (2.1)	2.1 (2.1)	2.9 (2.8)
Anxiety score (0–21)[8]	**2.9 (2.6)**	**5.3 (2.6)** [12]	**6.0 (3.3)** [12]
Autonomic index (0–30)[9]	**1.5 (1.4)**	**5.7 (5.0)** [13]	**6.3 (3.3)** [13]

Controls (C), SM: Sleep-related migraine attack subgroup. NSM: non-sleep-related migraine.
[1]Awakenings lasting more than 30 minutes.
[2]Awakenings lasting less than 30 minutes.
[3]Categorized as 0: <15 min, 1: 15–30 min, 2: 30–90 min, 3: > 90 min.
[4]Sum of four insomnia-questions in KSQ (Karolinska sleep questionnaire).
[5]Pittsburgh sleep quality index.
[6]frequency of pain-related sleep problems during the last month from the PSQI questionnaire. [7]Restless legs (1 = answered yes to all four obligatory criteria).
[8]Sum of seven questions about depression and anxiety symptoms respectively during the last week from the Hospital Anxiety and Depression Scale (HADS) questionnaire.
[9]Sum of 10 questions about palpitations, nausea, unsteadiness, muscle weakness, tremulousness, dizziness, blurred vision, shivering, and paleness.
[10]Diary data lacking from one NSM subject.
[11]NSM or SM ≠ C ($p < 0.05$). [12] NSM or SM ≠ C ($p < 0.01$). [13] NSM or SM ≠ C ($p < 0.001$). (Mann–Whitney U-test). Significant differences are emphasized with bold types.

Discussion

In this first prospective exploratory case–control study evaluating NSM- and SM patients and controls, we found that NSM had increased objective sleep quality, increased subjective daytime tiredness and reduced PT. The SM patients on the other side had signs of reduced objective sleep quality, but had normal PT and did not report increased subjective daytime tiredness.

NSM

NSM patients had increased daytime tiredness, more SWS (N3) sleep, less fast arousals and a higher K-burst index than controls. After sleep deprivation in healthy controls increased amount of K-complexes [37] and SWS [37,38] and reduced amount of fast arousals [38] are found. However, based on the sleep diaries the NSM patients had the same sleep times as the SM patients and controls. A higher need of sleep and a relative sleep deprivation among the NSM patients could be one explanation. Another explanation could be hypoarousability, i.e. hypofunction of the CNS arousal system [14].

The lower caffeine intake among NSM patients can possibly be related to the daytime tiredness. However, reduced caffeine intake is unlikely to explain our PSG findings among NSM patients because a low-to-moderate amount of caffeine has been found to have little effect on subjective and objective sleep apart from more stage I sleep (Rechtschaffen and Kales) in insomniacs [39].

We also found reduced TPT among the NSM patients. Reduced PT has previously been found among sleep-deprived healthy persons [17-20]. In addition, EEG has in several old studies been found to resemble drowsiness in several migraineurs [40]. These observations do also fit with our interpretation of the present data, i.e. that the NSM patients may be hypoaroused and suffer from (relative) sleep deprivation.

Moreover, there were negative correlations between N3 sleep and PPT and between KD-bursts and TPT among the NSM patients. Slow bursts are said to reflect the slow wave sleep propensity, occurring with highest frequency before SWS in the first sleep cycles [41]. Hence, increased SWS and slow bursts could indicate a higher need for sleep in NSM patients compared to SM patients. Our findings do also suggest a possible dose–response relationship between the proposed sleep deprivation and the reduced PT.

SM

The SM patients had no signs consistent with sleep deprivation (e.g. increased daytime tiredness and reduced

Table 3 PSG sleep quality, and pain threshold mean values (SD) for controls, and interictal migraine subgroups

	C (n = 34)	SM (n = 15)	NSM (n = 18)
Time in bed	**453 (58)**	465 (57)	**488 (46)[4]**
Total sleep time (min)	409 (68)	417 (67)	451 (52)
Sleep efficiency (%)	90.0 (8.1)	89.4 (7.6)	92.4 (4.2)
Latency to sleep onset (min)	12.8 (14.6)	13.8 (25.1)	7.4 (7.7)
Awakening index (no/h)	**0.99 (0.59)**	**1.45 (0.84)[4]**	1.12 (0.63)
Wake after sleep onset (min)	30.9 (26.7)	34.5 (19.0)	29.5 (16.4)
Stage N1 (min)	**27 (19)**	**35 (17)[6]**	29 (13)
Stage N2 (min)	197 (47)	194 (44)	206 (45)
Stage N3 (min)	**86 (31)**	**88 (25)[3]**	**104 (28)[3,5]**
REM (min)	99 (26)	99 (38)	112 (32)
SaO2 mean (%)	**95.2 (1.4)**	**95.2 (1.4)[3]**	**96.1 (1.0)[3,4]**
Apnea-hypopnea index (per hour)	2.7 (3.3)	2.6 (2.6)	2.2 (3.3)
Periodic limb movement index (per hour)	6.7 (10.3)	4.0 (6.3)	8.4 (11.4)
Fast arousal index (per sleep hour)	**18.3 (5.7)**	17.4 (8.6)	**15.5 (9.7)[4]**
Fast arousal index (per hour REM sleep)	21.8 (8.7)	21.3 (11.3)	18.2 (14.6)
KD-burst index (per sleep hour)	14.8 (10.9)	9.6 (7.3)	15.4 (9.8)
D-burst index (per sleep hour)	**11.8 (8.0)**	**7.3 (5.7)[4]**	11.3 (8.3)
K-burst index (per sleep hour)	**3.0 (3.8)**	**2.4 (2.2)[3]**	**4.0 (2.5)[3,4]**
PPTavg[1] (kPa)	**661 (249)**	586 (141)	**519 (125)[6]**
HPTavg[2] (°C)	**13.6 (3.1)**	12.6 (3.3)	**11.2 (3.7)[4]**
CPTavg[2] (°C)	**20.7 (6.3)**	18.3 (6.3)	**16.1 (7.4)[4]**

C: Controls, SM: Sleep-related migraine attack subgroup and NSM: non-sleep-related migraine recorded in an interictal phase. PPT: pressure pain threshold, HPT: Heat pain threshold, CPT: cold pain threshold. avg: Regional averages from either [1]splenius, trapezius, temporalis, and index finger or [2]forehead and palm. HPT and CPT are expressed as differences from the 32°C baseline.
Mann–Whitney U-test: [3]NSM ≠ SM ($p < 0.05$). [4]NSM or SM ≠ C ($p < 0.05$). [5]NSM ≠ C ($p < 0.01$), [6]NSM or SM ≠ C ($p = 0.05$). One control and two NSM subjects were excluded from the PLM analysis and one SM from arousal analysis because of loosened electrodes. Significant differences are emphasized with bold types.

PT) even though we found signs of disturbed sleep compared to controls. Age-adjusted headache duration in years was related to a distinct reduction of SWS among SM patients. Also, increasing insomnia symptoms were mainly related to reduced N2 sleep and there was an association between reduced N2 sleep and reduced PT. Furthermore SM patients also had fewer K-bursts than NSM patients. In coherence with findings of Della Marca [14] SM patients also had fewer D-bursts than controls. Slow bursts are frequent before and during SWS [41]. If slow bursts can be interpreted as a measure of the ability to get enough SWS, it also is consistent with a reduced ability to achieve sufficient SWS among SM patients. N2 sleep then might partially compensate for a possible lack of SWS in SM patients.

Nightly hypoxia is related to headache and tiredness [11] and SM patients had a slightly lower mean SaO2 during the whole night than NSM patients. However, mean SaO2 did not differ in SM patients compared to controls, and we could not detect any significant difference in the apnea- hypopnea index between these groups.

What is the importance of headache onset time?

In our first paper from this study [23], interictal migraineurs had increased amount of awakenings during sleep, but paradoxically tended to have less fast arousals and more slow wave sleep. From the present results we can see that the explanation is subgroup differences. The SM patients had increased awakenings and the NSM patients had increased slow wave sleep and less fast arousals.

A migraine attack may be interpreted as an example of genetically determined adaptive behavioral response to internal or external stressors that it is orchestrated by a threatened brain [42]. Also in the present study both SM and NSM had increased "load" with more symptoms of sleep disturbances and anxiety compared to controls [43,44]. Increased neural activity can increase sleep need [45], but we could not detect differences in work frequency, physical activity, affective or sleep symptoms between the NSM and SM groups.

Why were the SM patients not equally or more tired than the NSM patients? In line with Cortelli [42] we found signs of slightly disturbed sleep among SM patients

Table 4 Partial age-adjusted correlations[1] between sleep, symptoms, pain thresholds, among interictal migraineurs subgroups

	Sleep quality		Pain thresholds			Headache		
NSM (n = 18)	**Insomnia[2]**	**PSQI[3]**	**PPT**	**HPT**	**CPT**	**Headache days[4]**	**Headache intensity (1–4)**	**Headache duration (years) [1]**
Sleep N1	0.12	0.41	0.16	0.02	0.16	**0.60***	0.21	0.35
Sleep N2	0.18	0.26	0.29	−0.05	−0.04	0.18	0.08	−0.11
Sleep N3	−0.40	−0.47(*)	**−0.50***	−0.18	−0.21	−0.24	0.03	−0.23
REM sleep	−0.15	−0.25	−0.04	0.08	−0.27	0.21	0.19	0.03
Fast arousal index	0.46(*)	0.45(*)	0.30	−0.19	−0.23	−0.34	−0.10	0.09
Slow arousal (KD-) index	0.13	−0.33	0.05	**−0.57***	**−0.57***	**−0.64****	−0.01	−0.46(*)
SM (n = 15[5])	**Insomnia[2]**	**PSQI[3]**	**PPT**	**HPT**	**CPT**	**Headache days[4]**	**Headache intensity (1–4)**	**duration (years)**
Sleep N1	0.32	0.28	0.07	−0.12	0.08	0.11	0.19	−0.13
Sleep N2	**−0.69****	−0.46(*)	**0.54***	−0.20	0.08	−0.50(*)	0.04	0.28
Sleep N3	0.41	0.33	−0.36	−0.11	−0.44	0.39	−0.22	**−0.63***
REM sleep	−0.13	−0.11	0.15	0.10	0.34	−0.40	−0.01	−0.06
Fast arousal index	0.30	0.26	0.15	−0.21	−0.08	−0.02	0.18	−0.53(*)
Slow arousal (KD-) index	−0.36	−0.01	0.53(*)	−0.19	−0.31	0.05	0.40	−0.12

NSM: Non-sleep related migraine. SM: sleep related migraine.
[1]All variables were square root transformed before correlation was computed. SM: Sleep-related migraine attack subgroup and NSM: non-sleep-related migraine recorded in an interictal phase. PPT: pressure pain threshold, HPT: Heat pain threshold, CPT: cold pain threshold.
[2]Sum of four insomnia-questions in KSQ (Karolinska sleep questionnaire).
[3]Pittsburgh sleep quality index frequency of pain-related sleep problems during the last month from the PSQI questionnaire.
[4]Headache days last three months.
[5]One SM excluded from fast and slow arousal scoring because of loosened electrode.
$p < 0.10$(*), $p < 0.05$*, $p < 0.01$** Significant differences are emphasized with bold types.

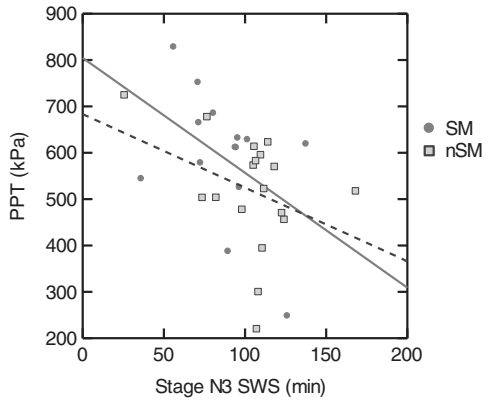

Figure 1 Pressure pain thresholds and amount of slow wave sleep (SWS) in sleep related migraine (SM, solid line) and non-sleep related migraine (NSM, dotted line). Less N3 sleep was significantly associated with high pressure pain thresholds in the NSM group (age adjusted r = −0.50. $p < 0.05$).

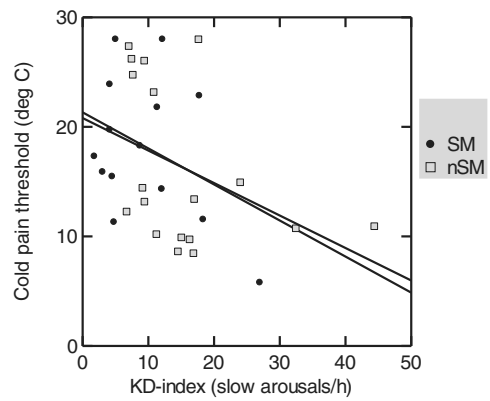

Figure 2 Cold pain thresholds and D-burst index in sleep related migraine (SM, solid line) and non-sleep related migraine (NSM, dotted line). Cold pain threshold is expressed as the difference from baseline. KD-bursts are significantly associated with cold hyperalgesia (age-adjusted r = −0.59, $p < 0.01$).

and signs indicating that daytime is more tiring for NSM patients than controls. It can be hypothesized that the lack of response decrement to repeating stimuli (habituation) described among migraineurs [46] might chiefly be a characteristic sign of NSM patients.

The apparently preserved arousability among SM patients might in fact be sign of high resistance towards daytime load consistent with the idea that SM patients do not reach their overload limit before nighttime. The negative effect of high arousability might be an increased vulnerability to reduced sleep quality in SM patients. It is possible that small disturbances in sleep quality (that normally are not perceived as sleep disruptive) are the drops that makes the flood in these patients; i.e. triggering a migraine attack during night. This notion fits with the parallel increase in sleep disturbances and sleep related migraine with age [47] and with the proposal that apnea disrupted sleep also can trigger a migraine attack [48].

The "hypoarousability" of the NSM and robust arousability among SM could in principle be related to the periaqueductal gray matter, a structure which is assumed important in the migraine pathogenesis [49], since "hypoarousal" and "hyperarousal" has been linked to ventrolateral and lateral regions respectively [50].

Strengths and limitations

The strength of this study is the blinded, controlled, prospective, and population based design, thereby also avoiding hospital-based severe and longstanding migraine cases.

There are different arousal definitions: AASM accepts only fast arousals [32]. Phase of transient activation (PAT) [33] is another definition of fast arousals. Low frequency episodes as D- and K-bursts are found related to temporarily increased heart rate and scored separately as arousals before [33]. The CAP system includes beneficially both fast and slow arousals in one scoring system [51] and is also previously used in examination of sleep among sleep-migraineurs [14]. However, CAP scoring covers only NREM sleep, is quite complicated to score [52] and sleep-migraineurs' sleep is previously also investigated without CAP scoring [15]. In the present exploratory study we included both fast and slow arousals as in the CAP system, but we intended to score both fast and slow arousals separately, without considering sleep phase and the time interval between the different arousal episodes.

Only one PSG recording from each patient in the present study excluded the possibility to evaluate intra individual changes in different migraine phases. A possible first night effect on slow D- and K-arousal bursts and fast microarousal bursts was non-significant and very small in one study [53]. Besides, any other systematic first night-effects would probably affect groups in a similar way and accordingly be cancelled out in a statistical comparison. Our method for separating migraineurs into SM- and NSM patients by one question on the most typical headache onset time is a weakness. A more objective way would be to evaluate headache onset in diaries for several months. However, as we only had diaries for four weeks, this alternative was not possible in the present study.

Furthermore no corrections for multiple comparisons were done because the study was exploratory, and we did not want to increase type II failures on the cost of reducing type I failures [36,54]. However, the chosen approach does increase the risk of false positives (type I errors) and our findings should accordingly be independently reproduced before firm conclusions can be drawn.

Conclusion

In conclusion, in this first prospective exploratory case–control study evaluating sleep in interictal SM- and NSM patients and controls, we found small, but probably important differences. NSM patients showed a sleep pattern consistent with foregoing sleep deprivation even if sleep times in sleep diaries were normal. SM patients on the other hand, had signs of slightly disturbed sleep. As far as we know, no others have compared PSG-sleep between NSM and controls. However, our results need independent confirmation.

Competing interest

The authors declare that they have no competing interest.

Authors' contribution

ME mounted some PSGs and performed some pain threshold measurements, analyzed all PSGs, performed the statistical analysis, prepared the initial draft and was the main author of the present manuscript. KH included patients in the study. GG was contact person for the participants, handled and typed all questionnaires. TS had the original idea of the study; he has made all the data files for statistics and been the main supervisor in all processes. All authors have contributed to the practical plans for the study, read, revised and approved the final manuscript.

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Article III

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Sleep quality, arousal and pain thresholds in tension-type headache: A blinded controlled polysomnographic study

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Abstract

Introduction: We aimed to compare subjective and objective sleep quality in tension-type headache (TTH) patients and to evaluate the relationship between sleep quality and pain thresholds (PT) in controls and TTH patients.

Methods: A blinded cross-sectional study where polysomnography (PSG) and PT (to pressure, heat and cold) measurements were done in 20 patients with TTH (eight episodic (ETTH) and twelve chronic (CTTH) TTH) and 29 healthy controls. Sleep diaries and questionnaires were applied.

Results: TTH patients had more anxiety ($p = 0.001$), insomnia ($p < 0.0005$), daytime tiredness ($p < 0.0005$) and reduced subjective sleep quality ($p < 0.0005$) compared to healthy controls. Sleep diaries revealed more long awakenings in TTH ($p = 0.01$) but no total sleep-time differences. TTH patients had more slow-wave sleep ($p = 0.002$) and less fast arousals ($p = 0.004$) in their PSGs. CTTH subjects had lower pressure PT ($p = 0.048$) and more daytime sleepiness than the controls ($p = 0.039$). Among TTH lower cold PT (CPT) correlated inversely with light sleep (N1) ($r = -0.49$, $p = 0.003$) while slow arousals correlated inversely with headache-frequency ($r = -0.64$, $p = 0.003$).

Conclusions: We hypothesize that TTH patients need more sleep than healthy controls and might be relatively sleep deprived. Inadequate sleep may also contribute to increased pain sensitivity and headache frequency in TTH.

Keywords

Tension-type headache, sleep, polysomnography, arousals, pain thresholds

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Introduction

Tension-type headache (TTH) is the most prevalent headache condition in the general population (1). Nevertheless, few studies have looked into the pathophysiology of the disorder (2), especially with a view to sleep disturbance. It has been shown that headache-free individuals with insomnia had increased risk of developing TTH 11 years later (3), and that TTH was associated with subjective sleep disturbances in general (4). Regarding the characteristics of TTH-associated sleep disturbances, only a few polysomnographic (PSG) studies in adults have been published (5–7) and arousals have not been quantified.

Sleep deprivation seems to reduce pain thresholds (PT) (8–10). Hence, mapping the relationship between sleep quality and PT of chronic and episodic TTH patients may have implications for understanding the pathophysiology of TTH.

Our main aim was to compare subjective and objective sleep quality variables and PT in headache-free controls and TTH patients in general. Secondly, we wanted to assess the association between sleep variables and headache severity and PT. A secondary subgroup

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analysis comparing episodic TTH (ETTH) and chronic TTH (CTTH) was also performed.

Methods

Subjects

In this cross-sectional study we recruited study subjects and controls by advertising in local newspapers for people between 18 and 64 years with and without headache. In addition, healthy blood donors were recruited as controls (CO) and 26 participants in a previous study were also invited. A nurse trained in headache research screened volunteers by a telephone interview followed by a consultation with a headache specialist who verified the diagnoses. We diagnosed the patients according to the International Headache Society (IHS) 2004 criteria (11). Subjects with episodic (ETTH) (1–15 headache days per month) or chronic (CTTH) (≥15 headache days per month) TTH were selected for the present study. Inclusion and examination were done in 2005 to 2007 and data analysis was done from 2009 to 2012. Exclusion criteria were coexisting frequent migraine, other major health problems (sleep disorder, hypertension, infection, neoplastic disease, neurological disease, central nervous system (CNS) implants, cardiac or pulmonary disease, chronic or acute pain, regular use of neuroleptic, antiepileptic and antidepressive drugs, hypnotics, analgesics, or use of migraine prophylaxis drugs for the last 4 weeks before inclusion) or pregnancy. Over-the-counter drugs (NSAIDS and paracetamol) for acute pain were allowed. We enrolled 126 persons, 85 women and 41 men. Results from 53 subjects with migraine have been reported in another paper (12). Four out of 24 subjects with TTH were excluded for technical reasons (battery error or lost electrodes, $n=2$) or moderate or severe sleep apnoea defined as apnoea hypopnoea index (AHI) >15 ($n=2$).

Twenty TTH patients and 29 controls comparable for age and sex were included in this study (Table 1). None used analgesics on the day before examination and only one participant, a TTH patient, used NSAIDs on the day of the examination.

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

Questionnaires and diaries

Every subject answered several questionnaires including Epworth sleepiness scale (13), Karolinska sleep questionnaire (KSQ) (14) and Pittsburgh sleep quality index (PSQI) (15). The nine PSQI questions indicating the frequency of common sleep problems (0–3), were summed into a combined global score variable (PSQIgs, possible range 0–27). A question about bothersome tiredness (Do you have bothersome tiredness during daytime?) was categorized as: none, <7 days per month, 7–14 days, >14 days per month, daily (0–4). We also applied questions targeting the occasional occurrence of the four obligatory restless legs criteria (urge to move the legs, rest worsens the

Table 1. Background and headache-related data for participants in the present study: Counts or mean (sd). No significant differences.

	Controls (n=29)	Tension-type headache (n=20)
Age (years)	41.2 (13.6)	40.9 (13.5)
Sex: F/M	15/14	11/9
BMI[a] (kg/m^2)	25.4 (3.2)	23.4 (3.5)
Caffeinated beverages (cups per day)	4.3 (3.6)	2.7 (2.2)
Alcohol: 0 (never) to 5 (4 or more per week)	3.0 (1.0)	2.5 (1.3)
Nicotine: no/yes	23/6	20/0
Physical activity[b]	1.7 (1.2)	1.6 (1.4)
Married/ common-law partner or single	22/7	16/4
Days since last menstruation	16.7 (9.2)	11.3 (6.4)
Headache time in diary (h/day)	na	13.3 (9.9)
Headache frequency (1–4)	na	3.5 (0.7)
Headache intensity (1–4)	na	1.5 (0.5)
Headache history duration (years)	na	15.8 (12.2)

[a]BMI= Body mass index. [b]Sum of scores for exercising/working out and for walking to workplace (0: seldom, 1:1–2 times/week, 2: At least 3 times/week; range 0–6). na: not applicable. Significant differences were not found.

urge, symptoms improve with movement, symptoms worsen in the evening or night) (16), categorizing those who answered 'yes' to all four questions to have restless legs symptoms. To evaluate symptoms related to the autonomic nervous system we used a subset of 10 questions (No. 26–35), answers ranged from 0 to 3, from the Autonomic Symptom Profile. Total score was summed 0 to 30 (17). Hospital and Anxiety Depression Scale (HADS) subscores, each based on seven of the 14 questions were calculated (18). The TTH patients quantified their headache time per month, their usual pain intensity and length of their headache attack (Table 1). All participants filled in a graphic sleep diary for 2 weeks before and after PSG. Sleep latency in the diary was categorized as 0: <15 min, 1: 15–30 min, 2: 31–90 min, 3: >90 min. Subjects in the headache group also completed a headache diary for this period. From diaries the average total sleep time, sleep latency, long (≥30 min) and short (<30 min) awakenings per night as well as headache hours per day were calculated and analyzed for the 14 days preceding the PSG registration. This categorical approach was chosen because it was deemed to adequately reflect the limited accuracy of the raw data (participants used a pencil to shade sleep hours in rows of 1-hour boxes (each row did represent 24 hours) in the printed sleep-diary form).

PSG

Patients and controls underwent a full night sleep registration with ambulatory equipment. They slept unattended in our patient-hotel in the neighbour building. PSG was recorded by a Notta recorder (EEG Technology Int.bv, Leveroy, the Netherlands) and analyzed with Stellate Harmonie software (Stellate, Montreal, Que., Canada). Eight EEG electrodes were placed according to the International (10-20) system (19) (F3, F4, C3, C4, P3, P4, O1, O2 plus Pz reference and Cz ground); two electrooculographic electrodes (EOG) applied 2 cm lateral and, respectively, 2 cm up and 2 cm down from the right and left lateral eye cantus. EOG-reference electrodes were applied to the left (A1) and the right (A2) mastoids. Surface electromyography was registered from submental muscles, the left anterior tibial muscle and trapezius muscle bilaterally.

The following sensors from Breabon Medical Corporation, Ontario, Canada were applied for respiration and circulation measurements: a three-point oronasal airflow thermistor (Airflow temperature sensor R-510), bands around thorax and abdomen to measure respiratory movements (Ultima Respiratory Effort Sensor, piezo-electric crystals) and a body position sensor (Ultima Body Position Sensor). An infrared index finger oximeter (model 8000J3, Nonin Medical Inc, Plymouth, MN,USA) and 10 mm silver chloride cup ECG electrodes (Natus Medical Inc, San Carlos, CA, USA) were also used. The participants were instructed to go to bed as usual, and write down light-off and light-on times using a synchronized wrist watch.

PSG data analysis. Analyses were performed from noted time for 'lights off' in the evening to 'lights on' in the morning. Respiratory events were scored automatically and edited visually later. The American Academy of Sleep Medicine (AASM) manual for the scoring of sleep and associated events from 2007 suggested two hypopnoea definitions based on nasal pressure signals (20), but we had a thermistor. Therefore, we chose to analyze hypopnoea according to a modified 'Chicago criteria' (21) (either 50% reduction in thermistor signals alone or at least 30% reduction associated with 4% desaturation).

Automatic periodic leg movement (PLM) analysis was implemented according to the AASM criteria (20). Manual sleep scoring, arousal scoring and event editing were performed by the first author (specialist in clinical neurophysiology), consulting a sleep expert (the last author) if in doubt. The inter rater reliability range for the 12 most relevant PSG-sleep variables in 20 incidental polysomnograms was found to be 0.762 to 0.997, and the mean intraclass coefficient of reliability was equal to 0.886. Sleep staging and arousal scoring was performed according to the AASM Manual (20) with a few exceptions, as described below.

First, fast arousals were defined according to the AASM manual (20) as an abrupt shift of EEG frequency (alpha, theta and/or faster than 16 Hz activity) lasting 3 to 30 seconds, separated with at least 10 seconds of sleep.

Second, we scored two additional PSG measures of slow-wave arousal: (a) Delta-bursts (D-bursts), defined as a sequence of delta waves lasting 2 s or more and exceeding the background amplitude with at least one-third (22), and (b) K-bursts, defined as at least two consecutive K-complexes (22). Awakening-, arousal-K- and D-burst-indexes were calculated as event number per sleep hour. As K- and D-bursts probably reflect similar physiological processes (23), they were combined into a KD-index for correlation analysis in the present paper. Further arousal scoring details have been published previously (12).

Pain thresholds. Thermal PT (TPT) and pressure PT (PPT) (algometry) were recorded 1 hour before the participants had their polysomnography equipment mounted. Heat and cold PT (HPT and CPT) were measured separately in a fixed order on the palmar hand

(thenar eminence) and the medial forehead on both sides with methods of limits (thermode area 25 mm × 50 mm, MSA, Somedic Sales AB, Sweden). The temperature was increased and reduced by 1°C/s from a 32°C baseline (warm range: 32–50°C, cold range 32–5°C). PPT was measured at four bilateral sites in a fixed order: m. temporalis (10 mm lateral to the external angle of the orbit), m. splenius (C2 level just at the edge of the trapezius muscle about 35–40 mm lateral to the midline), m. trapezius (10 mm lateral to the midpoint of a line connecting the acromion and the spinous process of C7), and over the distal phalanx of the middle finger (Algometer type II, probe area 1 cm^2, Somedic Sales AB, Sweden). Pressure was increased by 30 kPa/s. Threshold measurements were repeated three times, the left before the right side, and the averages were calculated. In subjects who did not feel cold pain at 5°C, 4°C was used in the analysis. PPT on the right and left sides were averaged for the present study. For correlation analysis we used the PPT average from the four sites and we used the PT difference from baseline HPTd (HPT-32) and CPTd (32-CPT), averaged from the head and hand sites.

Blinding

The technicians mounting PSG and testing PT were blinded for diagnoses. Scoring of the PSG data was also performed blinded for diagnoses. Two nurses administered the participant appointments and questionnaires and instructed the participant not to tell the technicians anything that could reveal their headache trait or state.

Statistics

Several variables had non-normal distributions and univariate two-group comparisons were made by non-parametric Mann-Whitney tests. Categorical data were analyzed with Pearson χ^2 test or Fisher's exact test if any cross tab cells had expected count less than five. Univariate comparisons were performed between CO and TTH groups, and between CO, CTTH and ETTH subgroups. Two-sided p-values less than 0.05 were regarded as significant.

Exploratory bivariate correlations were done with age-adjusted partial correlation calculated from square root transformed variables. Age-adjustment was performed to control for confounding effects on clinical variables (e.g. headache history) and sleep quality as sleep normally becomes more light with increasing age (24).

The power in Student's t-test for independent samples to detect a medium effect size equal to 0.8 SD in two-group comparisons was 79% for the CO–TTH comparison. The power to detect a large effect size equal to 1.2 SD was 75% for the CTTH-ETTH comparison.

Statistical analyses were performed with PASW statistics v.18 and SYSTAT version 11.

Results

Compared to controls, the TTH group reported more long awakenings during sleep ($p = 0.01$), more frequent daytime tiredness ($p < 0.0005$), more insomnia ($p < 0.0005$), reduced sleep quality in PSQI ($p < 0.0005$), more pain-related sleep trouble in the PSQ questionnaire ($p = 0.002$), more restless legs symptoms (45% vs. 14%, Fisher's exact $p = 0.022$), more anxiety ($p = 0.001$) and more autonomic symptoms than controls ($p < 0.0005$) (Table 2). Epworth sleepiness scale scores tended to be slightly higher in the TTH patients (Table 2), and the difference was significant for the CTTH subgroup compared with controls ($p = 0.04$). ETTH-CTTH symptom differences were non-significant except for a lower physical activity score in ETTH compared with CTTH and controls ($p = 0.048$ and $p = 0.042$, respectively).

The TTH group had more slow wave sleep (SWS, defined as stage N3; $p = 0.002$) (Table 3, Figure 1) and had less fast arousals ($p = 0.004$) than controls. The D-burst index was lower in CTTH compared with controls ($p = 0.016$) and to ETTH ($p = 0.04$) (Table 4). ETTH-CTTH sleep-quality differences in PSG were all non-significant. Periodic leg movements did not differ between groups (Table 3).

The TTH group also non-significantly tended to have lower PPT than controls ($p = 0.08$) and the difference between CTTH and headache-free subjects was significant ($p = 0.048$; Table 4).

For age-adjusted data we found significant inverse correlations between KD-burst index and headache frequency (Table 5) and between CPT and light (N1) sleep ($r = -0.49$, $p = 0.03$). There were also significant positive correlations between insomnia and anxiety both in controls ($r = 0.59$, $p = 0.001$), and in TTH patients ($r = 0.52$, $p = 0.024$) (Figure 2).

Discussion

Our main results were that TTH patients reported subjectively reduced sleep quality, whereas sleep diaries revealed normal sleep times and PSG had signs of increased sleep quality (i.e. increased SWS).

The subjective feeling of insufficient sleep is a well-known feature in TTH (4,25,26), but more detailed mapping with sleep diaries and PSG has seldom been reported. Although headache fluctuations in TTH patients have been related to short sleep in diaries

Table 2. Sleep diary, sleep disorder symptoms emotional state mean values (SD). Significant differences are marked with * or #.

	Controls (n = 29)	Tension-type headache (n = 20)
Average diary sleep time (hour)	7.2 (0.8)	6.8 (1.1)
Long awakenings in diary (no)	0.1 (0.2)	0.4 (0.4)*
Sleep latency in diary (0–3)[a]	0.4 (0.4)	0.6 (0.6)
Epworth sleepiness scale (0–24)	5.9 (3.2)	7.5 (3.9)
Daytime tiredness frequency (0–4)	0.7 (0.9)	1.7 (1.0)***
Snoring/apnea KSQ score (0–8)	1.9 (1.6)	1.2 (1.2)
Restless leg symptoms[b]	4/25	9/11#
Insomnia KSQ score (0–16)[c]	3.4 (2.4)	7.9 (2.4)***
PSQIgs (0–21)[d]	3.9 (2.7)	7.2 (3.2)***
HAD depression score (0–21)[e]	1.5 (2.2)	2.8 (3.0)
HAD anxiety score (0–21)[e]	3.0 (2.8)	5.9 (3.0)**
Autonomic symptom score (0–20)[f]	0.8 (1.1)	5.2 (3.4)***

[a]Categorized as 0: < 15 min, 1: 15–30 min, 2: 30–90 min, 3: > 90 min.
[b]Restless leg symptoms (answered yes to all four obligatory symptoms or not all four).
[c]Sum of the four insomnia-questions in KSQ (Karolinska sleep questionnaire).
[d]Pittsburgh sleep quality index (PSQI) global score.
[e]Sum of seven questions about depression and anxiety symptoms respectively during the last week from the Hospital Anxiety and Depression Scale questionnaire.
[f]Sum (0–20) of 10 questions (0–3) from the Autonomic Symptom Profile.
Significant differences TTH vs CO: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ (Mann-Whitney U-test), # Fisher exact test $p = 0.02$.

Table 3. PSG sleep quality mean values (SD). Significant difference is marked with **.

	Controls (n = 29)	Tension-type headache (n = 20)
Total sleep time (min)	401 (70)	432 (46)
Sleep efficiency (%)	89.8 (8.5)	91.2 (5.6)
Latency to sleep onset (min)	11.8 (14.6)	7.1 (6.8)
Wake after sleep onset (min)	32 (28)	34 (24)
Stage N1 (min)	28 (20)	29 (15)
Stage N2 (min)	191 (47)	185 (34)
Stage N3 (min)	84 (33)	107 (21)**
REM (min)	98 (27)	111 (30)
Apnea-hypopnea index (per hour)	3.0 (3.4)	1.9 (2.6)
Periodic limb movements index (per hour)*	7.7 (11)	3.6 (5.6)

*Available data in 28 CO and 17 TTH patients; **$p = 0.002$; (Mann-Whitney U-test).
Significant differences; CO vs. TTH.

(27) or long sleep in actigraphy (28), neither the average sleep duration in the diary nor the PSG-measured total sleep time differed between controls and TTH patients in the present study.

Furthermore, contradictory to their subjective symptoms, TTH patients in the present study also had increased SWS in PSG compared to controls, consistent with increased sleep quality (29) and similar to our recent findings in migraineurs (12). However, our results are contradictory to the results of Drake et al. (5) who described decreased total sleep time, increased awakening and very little SWS (5.1%) in an uncontrolled study of ten patients with 'muscle contraction headache'.

Subjective tiredness may be more related to lack of energy or fatigue than to sleepiness, as ESS scores were equal in the two groups. Lack of energy has been found previously in TTH patients (25,30). Daytime fatigue and subjective tiredness are also common features of insomnia (31,32). Insomniacs tend to resist falling asleep even though they are tired (33), possibly because emotional or physiological hyperarousal may counteract sleepiness despite lack of sleep (34). Insomnia is a headache trigger, a longitudinal risk factor for headache and a prevalent comorbid condition in TTH (3,4,35). However, subjects with known sleep disorders were not included in the present study. Many in our TTH group probably had lighter or subclinical insomnia symptoms and may not fulfil the diagnostic criteria.

TTH patients had more restless legs symptoms than controls. Severe restless legs symptoms may inhibit sleep onset (36), but insomnia is not among the obligatory criteria for the restless legs syndrome (RLS) diagnosis. Restless legs symptoms are frequent in the general population (prevalence of 4–10%), which is comparable with the prevalence of 14% (95% CI 11–26%) among our controls. However, only 1–3% seem to have a clinically significant restless legs syndrome (37). In the present study none of our participants had known RLS by inclusion and sleep latency was not prolonged among the TTH patients. The sleep disturbance in RLS has also been partly linked to periodic leg movements (PLM) in sleep, but the PLM index did not differ between TTH and control groups in the present study. Hence, although the restless leg symptoms in TTH patients were frequent (45% with 95% CI 34–58%), symptoms were probably still below the 'sleep disturbing threshold', that is conceptually related to the increased subjective symptoms of inferior sleep quality and insomnia (as measured with PSQIgs and KSQ) in our TTH group. As a parallel, a history of chronic insomnia does not always predict poor PSG sleep (38).

In accordance with previous findings, PPT was lower in CTTH patients compared with controls (2,39).

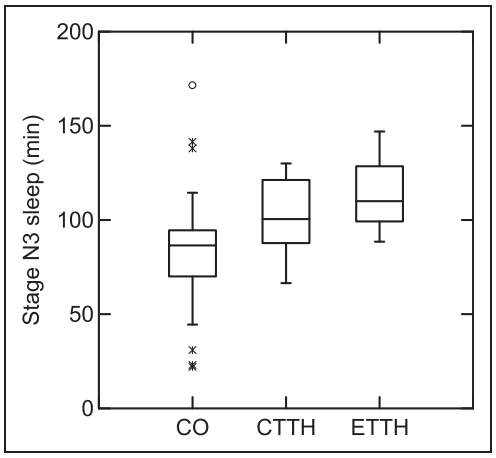

Figure 1. More slow-wave N3 sleep is observed in chronic (CTTH, $p = 0.03$) and episodic (ETTH, $p = 0.003$) tension-type headache subgroups compared to controls (CO). Boxes show median values, 25 and 75 percentile. Whiskers show the range apart from moderate and far outliers represented by * and o symbols respectively.

Reduced PPT has also been found after sleep deprivation (9). Among TTH we also found a negative correlation between light sleep (N1 sleep) and CPT. Hence, reduced sleep quality seems to increase the sensitivity to thermal pain in TTH. A significant HPT reduction has previously been found after sleep deprivation (8,10). Accordingly, it is possible that an unfulfilled need for sleep in TTH patients enhances the central sensitization that probably underlies PPT reductions in TTH patients (2).

TTH patients in the present study also had less fast arousals than controls. The PSG pattern of increased SWS and reduced frequency of fast arousals has also been found in healthy subjects during the night after sleep restriction (40). However, as sleep diaries revealed normal average total sleep times, we hypothesize that TTH patients need more sleep than headache-free control subjects. If this need is not satisfied, they may become relatively sleep-deprived. This hypothesis may also explain the apparently paradoxical coexistence of subjectively reduced sleep quality and objectively PSG-measured increase in sleep quality.

Table 4. PSG arousal and pain threshold mean values (SD) for controls, tension-type headache (TTH) and TTH subgroups. Significant differences are marked with * or #.

	Controls (n=29)	TTH (n=20)	CTTH (n=12)	ETTH (n=8)
Fast arousal index (per sleep hour)	19.2 (5.6)	14.5 (4.3)**	13.5 (4.7)	16.0 (3.3)
KD-burst index (per sleep hour)	14.4 (11.6)	11.7 (9.8)	8.6 (8.1)(*)	16.2 (10.9)
D-burst index (per sleep hour)	11.6 (8.6)	7.9 (6.3)	5.5 (4.3)*	11.5 (7.3)#
$PPTd_{avg}$[a] (kPa)	678 (251)	543 (191)(*)	506 (215)*	598 (144)
$HPTd_{avg}$[b] (°C)	13.5 (3.2)	12.7 (3.7)	12.4 (4.1)	13.2 (3.2)
$CPTd_{avg}$[c] (°C)	21.0 (6.2)	19.4 (7.4)	17.5 (7.9)	22.3 (5.6)

[a]PPTavg = Pressure pain thresholds average: Regional averages from either m. splenius, trapezius, temporalis, and index finger.
[b]$HPTd_{avg}$ and
[c]$CPTd_{avg}$ = Heat and cold pain threshold average difference from the 32°C baseline. $HPTd_{avg}$ and $CPTd_{avg}$ are the average for forehead and palm measurements.
Episodic (ETTH) and chronic (CTTH) tension-type headache. Significant differences; CO vs. TTH/CTTH/ETTH (*) $p<0.08$,*$p<0.05$, **$p<0.005$; ETTH vs CTTH #$p<0.05$ (Mann-Whitney U-test).

Table 5. Partial correlations (adjusted for age) and *p*-values in parentheses for associations between arousal and headache variables in TTH.

	Headache history duration	Headache frequency	Headache intensity
Fast arousal index (per hour)	−0.33 (0.17)	−0.24 (0.33)	0.10 (0.67)
KD-burst index (per hour)	−0.25 (0.30)	−0.64 (0.003)	0.24 (0.31)
Stage N3 (min)	−0.03 (0.92)	−0.27 (0.26)	−0.06 (0.82)

Calculations were performed on square root transformed variables. All partial correlations were non-significant except for headache frequency versus KD-burst index.

D-bursts were least frequent in the CTTH group whereas daytime sleepiness was also slightly increased in CTTH, suggesting that patients with the most severe headache also possibly were in most lack of sleep. A significant association between less KD-bursts and higher headache frequency was also found. Slow bursts are frequent before and during SWS (41). If slow bursts also can be interpreted as a measure of the ability to get enough SWS sleep, this ability might be protective against headache.

What is the likely mechanism behind the proposed need for more sleep in TTH patients?

Increased neural activity can induce increased sleep need (42). Both ETTH and CTTH had increased autonomic and anxiety symptoms. Strong correlation between anxiety and insomnia was observed both among TTH and controls. These observations suggest that the hyperarousal concept of insomnia also may be applicable in TTH patients. Some insomniacs probably have increased physiological arousal (43) and increased 24-hour metabolic rate compared with normal sleepers (44). Insomnia is also related to increased emotional reactivity (45) and stress (46). Subjective stress ('mental tension') is also one of the most conspicuous precipitating factors in TTH (47). Signs of increased CNS excitability in TTH patients have been found previously, although the findings are not quite consistent (48). Hence, we hypothesize that increased sleep need is secondary to lengthy emotional and autonomic physiological activation in TTH.

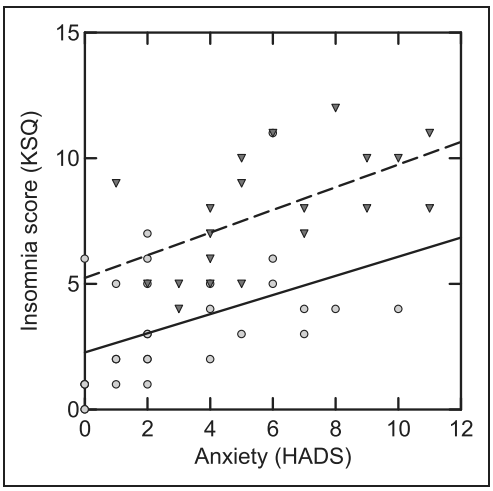

Figure 2. Insomnia symptoms correlated with anxiety both in controls (grey circles, continuous line, $p = 0.003$) and TTH patients (filled triangles, dotted line, $p = 0.005$).

Methodological considerations

The strong side of the present study is the blinded design where PT, subjective and objective sleep are analyzed together in both controls and headache patients. We have studied unrestricted sleep and these results should be compared with sleep studies after experimental sleep deprivation or sleep restriction with caution. The use of painkillers was very low and could hardly explain PT differences between the groups.

Arousal can be scored in different ways. Fast arousals are defined conservatively by the AASM (20), but they can also be defined more broadly to include highly overlapping concepts like microarousals, phase of transient activation (PAT) (22) and cyclic alternating pattern (CAP) A2 and A3. Low-frequency episodes as K- and D-bursts and CAP A1 are not accepted as arousals by AASM. However, both K- and D-burst are associated with heart rate increase (22) and incorporated into the CAP system (49). Because we intended to perform an open-minded and unbiased exploration, we scored arousals without considering the time between them (as opposed to the CAP system).

We had one ambulatory PSG recording per subject which might not be representative for over-time sleep for each subject. However, a possible 'first night effect' (a slightly reduced sleep quality in the first PSG-night) may be very slight in ambulatory PSG (50) and it should be identical in both groups. In this exploratory phase we have tested several hypotheses. We are fully aware of the possibility of making statistical type I errors and we acknowledge a need for independent replication. The ETTH and CTTH groups were small giving low power for the subgroup comparison. Although one may argue that significant differences in small groups must reflect large and possibly clinically significant effects, uncertainty about generalizability remains and independent confirmation in a larger sample is mandatory.

PT probably increase by age (51) and probably differ between the genders (52). If our purpose had been to assess individual abnormality rates, a larger age- and gender-stratified reference material would have been necessary. However, in the present study, our focus was on the comparison between TTH and non-headache groups and on the association between PT and sleep variables. Hence it was necessary and sufficient to recruit a control group with age and gender similar to the TTH group.

CPT seem to vary a lot interindividually (53). A substantial difference in inter-individual variability between various pain measures may make the physiological relevance of findings unsecure. Hence, larger groups are necessary in future studies to increase the precision of group-difference estimates in order to

properly evaluate and compare the relative differences between CPT, HPT and PPT in headache patients.

Conclusions

TTH patients have reduced subjective sleep quality and normal sleep times in PSG and diaries while PSG analysis revealed increased SWS time and reduced arousal density. These findings may suggest a foregoing sleep deprivation. A tendency to reduced PT among TTH patients is also consistent with sleep deprivation. Hence, we hypothesize that TTH patients are relatively sleep-deprived because of a greater need for sleep than healthy controls. Inadequate sleep may contribute to increased pain sensitivity and be a part of the TTH aetiology.

Clinical implications

- Tension-type headache patients have more subjective sleep disturbances than healthy controls, but normal sleep times in diaries.
- Tension-type headache patients have increased sleep quality in polysomnography.
- Tension-type headache patients might need more sleep than healthy controls.

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Conflict of interest

None declared.

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