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Martin Syvertsen Mykland

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The effects of insufficient sleep on brain function in migraine

Doctoral thesis

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Norwegian University of Science and Technology
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Søvn og hjernefunksjon hos personer med migrene

Migrene rammer omtrent 15 % av den voksne befolkningen. Det er en tydelig, men kompleks sammenheng mellom søvn og migrene. For eksempel kan søvnendringer utløse anfall mens søvn også kan bidra til å stoppe et pågående anfall. Vi kjenner ikke årsaken til koblingen mellom migrene og søvn. Vi har derfor utforsket hvordan søvnendringer påvirker hjernens funksjon hos personer med migrene og friske kontrollpersoner.

GABA er et signalstoff som demper aktiviteten i nerveceller. Lite søvn reduserte antatt GABA-aktivitet i hjernen hos personer med migrene mens de ikke hadde anfall. GABA-relatert aktivitet ble mest redusert hos personer som vanligvis har sterkere overfølsomhet for sanseinntrykk under anfall og kraftigere symptomer i forkant av anfall. Vi fant denne endringen i hjerne-aktivitet hos dem som vanligvis har anfall på dagtid og ikke hos dem som får anfall under søvn. Dette kan bety at migrene som kommer på natten har andre årsaker enn migrene som kommer på dagtid. Gradvis frem mot et anfall så vi en motsatt respons på redusert søvn hvor våre funn passer med at hjernens GABA-aktivitet økte.

Like etter et migreneanfall så vi endret hjerneaktivitet etter mindre søvn som ligner det man ser hos friske personer som holdes våkne hele natten. Dette kan bety at personer med migrene er mer sårbare for søvnmangel under eller like etter et anfall.

Studien ble gjennomført ved å måle mekanismer som kontrollerer hjernens funksjon etter to netter med vanlig søvn og to netter med redusert søvn. Dette gjorde vi hos 51 personer med migrene og 29 friske kontrollpersoner. Vi undersøkte hjernens elektriske aktivitet under og etter stimulering av sansesystemet, og hjernens respons til ulike typer magnetisk stimulering.

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Trondheim, April 2023 Martin Syvertsen Mykland

List of papers

Paper I

Sleep restriction alters cortical inhibition in migraine: A transcranial magnetic stimulation study

Martin Syvertsen Mykland, Martin Uglem, Jan Petter Neverdahl, Lise Rystad Øie, Tore Wergeland Meisingset, David W. Dodick, Erling Tronvik, Morten Engstrøm, Trond Sand and Petter Moe Omland

Published in Clin Neurophysiol 2022; 139: 28-42.

Paper II

Insufficient sleep may alter cortical excitability near the migraine attack: A blinded TMS crossover study

Martin Syvertsen Mykland, Martin Uglem, Lars Jacob Stovner, Eiliv Brenner, Mari Storli Snoen, Gøril Bruvik Gravdahl, Trond Sand and Petter Moe Omland

Published in Cephalalgia 2023;43(3).

Paper III

Effects of insufficient sleep on sensorimotor processing in migraine: A randomised, blinded crossover study of event related beta oscillations

Martin Syvertsen Mykland, Martin Uglem, Marte-Helene Bjørk, Dagfinn Matre, Trond Sand and Petter Moe Omland

Published in Cephalalgia 2023;43(3).

Role of the candidate

The study was planned as a combined effort by the candidate, supervisors, and other project participants. The candidate had the main role in initially organising a complete setup of the required equipment, performing pilots, and adjusting the hardware and software for completion of the protocol as planned. Recruitment was organised by the candidate and the main supervisor and carried out by study nurses and neurologists due to inclusion requirements and blinding procedures. All examinations, data analyses and statistical analyses were conducted by the candidate. The candidate wrote the complete first draft of all manuscripts, and were responsible for revising, completing and submitting the manuscripts. The candidate has presented the study and the results at international congresses and in relevant media including national television and radio.

Summary

Background

Migraine affects about 15 % of the adult population aged 15-64 years old. The combined large prevalence and considerable disability of migraine makes it the first cause of most years lived with disability below 50 years of age. Despite this enormous burden of the disease, the migraine pathophysiology is not yet understood.

The clinical association between migraine and sleep is described in literature dating back to the 17th century. However, the cause of this association has not been elucidated. Recent findings indicate that some regions and networks of the brain which are involved in sleep physiology, also constitute parts of the regions involved in migraine pathophysiology.

Dysregulation of thalamocortical excitability due to inhibitory or facilitatory mechanisms have been indicated to play a part in the migraine cycle pathophysiology. Inhibitory and facilitatory mechanism can be investigated using transcranial magnetic stimulation (TMS) and electroencephalography (EEG). The effect of sleep restriction on these measurements may provide new insight into the role of sleep in migraine.

We hypothesised that migraine patients have an underlying dysfunction of sleep-wake systems and thalamocortical excitability which would respond differently to changes in sleep compared to controls, throughout the migraine cycle and in sleep related migraine subgroups.

Methods

We examined 51 migraine subjects and 29 healthy controls after two nights of eight hour habitual sleep and two nights of four hour restricted sleep. We performed measurements using TMS and EEG to evaluate cortical silent period (CSP), short interval intracortical inhibition (SICI), intracranial facilitation (ICF), long interval intracortical inhibition (LICI), short latency afferent inhibition (SAI), beta-event related desynchronisation (beta-ERD) and beta-event related synchronisation (beta-ERS). Investigations and analyses were performed by a blinded investigator.

Main results

We detected reduced CSP duration after sleep restriction in interictal migraine. This finding was specific for the non-sleep related migraine subgroup and correlated with ictal symptoms of hypersensitivity and dopaminergic premonitory symptoms. In the sleep related migraine subgroup, LICI and beta-ERS was reduced after sleep restriction.

Before migraine attacks LICI was reduced after habitual sleep and increased after restricted sleep. SAI was decreased after sleep restriction preictally.

After attacks SICI and beta-ERS was reduced and ICF and beta-ERD increased after sleep restriction.

Conclusion

Migraine pathophysiology may encompass a dysfunction of GABA-B mediated inhibition interictally which responds abnormally to insufficient sleep. This dysfunctional GABAergic system seems to be regulated by dopaminergic modulation and hypothalamic mechanisms. Sleep and non-sleep related migraine pathophysiology may involve different types of alterations in GABA-B mediated inhibition. The GABAergic dysfunction appears to be further altered preictally and gradually towards attack commencement. Furthermore, sleep restriction during attacks may introduce a postictal brain dysfunction similar to what has been found in healthy subjects after total sleep deprivation. This finding indicates increased need for sufficient sleep during migraine attacks to maintain neurological functioning.

List of abbreviations

AMT	Active motor threshold
ANOVA	Analysis of variance
AP	Anteroposterior
APB	Abductor pollicis brevis muscle
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CM	Chronic migraine
CNS	Central nervous system
CO	Healthy control
CRH	Corticotropin-releasing hormone
CS	Conditioning stimulus
CSD	Cortical spreading depression
CSP	Cortical silent period
DC	Direct current
EEG	Electroencephalography
EM	Episodic migraine
EMG	Electromyography
EOG	Electrooculography
ERD	Event related desynchronisation
ERS	Event related synchronisation
ERSP	Event related spectral perturbations
FDI	First dorsal interosseus muscle
FHM	Familial hemiplegic migraine
fMRI	Functional magnetic resonance imaging

GABA	Gamma-aminobutyric acid
ICA	Independent component analysis
ICF	Intracortical facilitation
ICHD	The International Classification of Headache Disorders
IFCN	International Federation of Clinical Neurophysiology
IQR	Interquartile range
ISI	Interstimulus interval
ITI	Inter-train interval
LICI	Long interval intracortical inhibition
MA	Migraine with aura
MCD	Mean consecutive difference
MEG	Magnetoencephalography
MEP	Muscle evoked potential
MIG	Migraine
MN	Median nerve
MRBD	Movement related beta decrease
MRI	Magnetic resonance imaging
MSO	Maximum stimulator output
MT	Motor threshold
MVC	Maximum voluntary contraction
NMDA	N-methyl-D-aspartate
NSM	Non-sleep related migraine
PA	Posteroanterior
PACAP	Pituitary adenylyl cyclase-activation protein

PAG	Periaqueductal grey
PEST	Parameter Estimation by Sequential Testing
PET	Positron emission tomography
PMBR	Post-movement beta rebound
PVN	Paraventricular nucleus of the hypothalamus
REM	Rapid eye movement
RMT	Resting motor threshold
SAI	Short latency afferent inhibition
SICI	Short interval intracortical inhibition
SM	Sleep related migraine
TMS	Transcranial magnetic stimulation
TS	Test stimulus

1. Introduction

Migraine is a multifaceted brain disorder characterised by headache and a wide spectrum of symptoms occurring before, during and after the headache attack. Consequently, migraine is divided into phases representing different parts of the migraine cycle. Various pathophysiological properties pertaining to each of these phases have been discovered, but the underlying cause of migraine remains to be elucidated. The migraine diagnosis also allows for great variation in phenotype, possibly representing a spectrum of undiscovered migraine subgroups. Another enigma in the unsolved migraine conundrum is an apparent connection between sleep and migraine. Being able to explain this connection may be crucial for understanding the migraine pathogenesis. In this thesis, I elaborate on the interplay between sleep physiology and migraine pathophysiology, both for migraine in general as well as for proposed migraine subgroups.

1.1 Historical understanding of migraine

The earliest known accounts of headaches occurred several millennia ago, but the differentiation between types of headaches has for most of this time been unclear (Goadsby et al., 2017). However, descriptions of migraine-like headache dates back to the 17th century. In a 1683 publication, Thomas Willis described a case of headache starting in puberty of a woman, arising in episodes at its own accord, being both varying unilateral and bilateral, and causing avoidance of light and noise. The patient was forced to lie down during attacks with heavy and disturbed sleep and awakened with headache relief. The disease progressed to over twenty days of attacks per month before being almost continuous (Willis, 1683). Thus, he likely described what we now recognise as a typical evolution of episodic migraine turning chronic, with the well-known need for sleep during attacks.

The cause of migraine was thoroughly debated during the centuries following the descriptions of Willis. As migraine was not considered a part of conventional medicine, details of the disease often relied on personal accounts such as those by John Fothergill in the 18th century. He described migraine upon waking and sleep as an effective treatment of attacks (Pearce, 2013). Of great importance for advancing our understanding of the disorder was the theories of migraine pathophysiology by Edward Living and Peter Wallwork Latham during the 19th century. Liveing discussed connections between different paroxysmal conditions and "neurosal disorders," and suggested that "nerve-storms" could be a mechanism in migraine. Latham on the other hand, unified the hypothesis proposed by Du Bois-Reymond of increased sympathicotonic influence leading to unilateral vasoconstriction and the opposing

suggestion by Charles Edouard Brown-Séquard of a vasoparalytic migraine model (Weatherall, 2012, Liveing, 1873, Latham, 1873, Koehler, 1995). As Willis had already done, Latham described cases of headache with relief from sleep, followed by postdromal symptoms after awakening. He also mentioned loss of sleep as one of the common predisposing causes (Latham, 1873).

While the theories of Liveing differ from today's understanding of migraine, his arguments for a neural origin of the disorder are still relevant today. He also made several mentions of the importance of sleep in migraine. He described attacks being shortened and often terminated by sleep, as well as attacks commencing on awakening, sleepiness as an accompanying symptom and insufficient sleep as a trigger of migraine attacks. However, he refrained from attempting to explain the connection between migraine and sleep (Liveing, 1873), and this connection has largely remained unexplained to this day.

Harold Wolff had important influence on the migraine field from the 1930s and 1940s. He suggested that migraine aura was caused by cranial vasoconstriction based on the aura abolishing effects of amyl nitrite. Furthermore, he proposed that migraine headache was caused by cranial artery distention based on the observed effects of ergotamine. This theory became the common conception of migraine during the subsequent decades. Interestingly, Wolff did not comment on the previous suggestions by Latham which resembles his own or of Latham's autonomic explanation (Weatherall, 2012, Graham and Wolff, 1938, Wolff, 1948). Similar to Liveing before him, Wolff observed that sleep may be used as attack prevention and treatment (Blau, 2004).

After the 1940s, the cause of migraine headache was understood to be of vascular nature due to Wolff's contributions (Graham, 1952, Graham and Wolff, 1938). However, the underlying cause of this dysfunction was still unclear. Migraine was already then considered a familial trait, mostly affecting people either seeking stress or who were ill-equipped to handle stress. This suggestion was based on several observations including those of migraine patients being typically chronically fatigued perfectionists with habits of little rest and either insufficient or disturbed sleep (Graham, 1952).

While the vascular theory of migraine was prominent in the second half of the 20th century, other breakthroughs were made during this time. The involvement of serotonin in migraine pathophysiology was suggested by Frederigo Sicuteri and colleagues in the 1950s. This suggestion was based on observations of increased serotonin metabolite release and the effect

of a preventive combined serotonin agonist and antagonist (Solomon et al., 2008). This research also led to the suggestion that serotonin may be a central mediator of migraine, and that serotonin may not solely act peripherally (Sicuteri, 1973, Sicuteri, 1972). Various reports of electroencephalography (EEG) abnormalities in migraine also led to the use of antiepileptic drugs in migraine treatment in the 1960s (Solomon et al., 2008). The understanding that migraine aura was caused by vasodilation (Solomon et al., 2008), was also challenged when Milner in 1958 suggested that the spreading depression of Leão could be the cause of migraine aura (Milner, 1958) as previously also noted by Leão himself (Weatherall, 2021, Leao, 1944).

The current understanding of migraine pathophysiology is in part built on a further adapted combination of these earlier theories. The importance of sleep in migraine remains widely recognised but is still largely unexplained. In this thesis, I aim to further elaborate on this important relation, doing what Liveing considered in the 19th century but would not attempt.

1.2 Clinical features and epidemiology of migraine

Migraine affects a global average of about 15 % of the adult population aged 15-64 (Steiner et al., 2021). It is further estimated that 80 % of these individuals have significant disability due to the disease, making 12 % of the global adult population aged 15-64 years experiencing disability due to migraine. This enormous disease burden makes migraine the number one cause of disability below 50 years of age (Steiner et al., 2018).

1.2.1 The migraine diagnosis

As phrased by John W. Scott in the 1940s, headaches can be divided into three types: Headaches one can forget, headaches one cannot forget and headaches making one forget everything else. Migraine headache would fit in the last group (Scott, 1941). The Ad Hoc Committee on Classification of Headache progressed headache categorisation in 1962 with a classification of headache based on pain mechanisms. They simultaneously concluded that this story was far from complete (Friedman et al., 1962). In 1988, a further breakthrough in headache medicine came with the classification of headache types published by the International Headache Society, led by Jes Olesen (IHS, 1988, Olesen, 2008). The current version of The International Classification of Headache Disorders 3rd edition (ICHD-3) was published in 2018 (IHS, 2018). According to ICHD-3, the migraine without aura diagnosis (1.1) requires at least 5 attacks, untreated attack duration of 4-72 hours, either nausea and/or vomiting or photophobia and phonophobia, and at least 2 out of 4 migraine characteristics. These characteristics are unilateral location, pulsating quality, moderate or severe pain

intensity and aggravation by routine physical activity (IHS, 2018). Thus, the migraine diagnosis allows for variation in phenotype and heterogeneity within the disease category.

About 30 % of migraine patients experience migraine aura (Viana et al., 2018, Rasmussen and Olesen, 1992). The ICHD-3 criteria for the Migraine with aura (1.2) diagnosis require at least 2 attacks with one or more fully reversible aura symptoms. These symptoms can be visual, sensory, speech, language, motor, brainstem, and/or retinal. The aura must also possess at least 3 out of 6 characteristics. These characteristics are gradually spread of at least one aura symptom over at least 5 minutes, two or more aura symptoms in succession, each aura symptom lasting 5-60 minutes, at least one unilateral aura symptom, at least one positive aura symptom and aura being accompanied or followed within 60 minutes by headache. Furthermore, a diagnosis of migraine with typical aura (1.2.1) require the same criteria, but does not include motor, brainstem or retinal auras (IHS, 2018). Visual aura is the most common type occurring in about 98-99 % of cases, followed by sensory aura in about 31-36 % and dysphasic symptoms in about 10-18 %. Some migraine patients also exclusively experience migraine aura without headache. Headache usually follows aura, but simultaneous headache and aura have been described for about 4 % and aura following headache in about 3 % (Kim et al., 2022, Russell and Olesen, 1996, Viana et al., 2017).

1.2.2 Migraine phases

Migraine is by many considered a paroxysmal brain disorder which cycles between 4 different phases: The interictal, preictal, ictal and postictal phases. The exact duration and variation of these phases are not known. The ictal phase is usually defined as the migraine headache phase. The preictal phase is suggested to last up to 48 hours and occur prior to the commencement of the headache attack. Several premonitory or prodromal symptoms is described during the time overlapping with this preictal phase. The postictal phase is suggested to last up to 24 hours after the resolution of a migraine headache attack and overlap with the time when migraine patients may experience postdromal symptoms (Peng and May, 2020). A portion of migraine patients also report interictal symptoms between the postictal and preictal phase (Lampl et al., 2016).

Premonitory or prodromal symptoms of migraine has at least been known since the accounts by John Fordyce of his own migraine in *De Hemicrania* in 1758 (Pearce, 1986). Methods for assessing premonitory symptoms have been diverse with many retrospective studies and a large variation in reported symptom prevalence (9-88 %) (Karsan et al., 2018). One prospective study reported a premonitory symptom prevalence of 84 % (Quintela et al.,

2006), which indicate that such symptoms is likely very common. Premonitory symptoms are likely also often mistaken to be triggers of the attack by many migraine patients (Karsan et al., 2018). Among the most common premonitory symptoms are fatigue, sleep disturbances, yawning, concentration difficulties, stiff neck, mood change, irritability, anxiety, phonophobia and photophobia (Giffin et al., 2003, Schoonman et al., 2006, Karsan et al., 2018, Quintela et al., 2006, Kelman, 2004, Eigenbrodt et al., 2022). Premonitory symptoms have been shown to be more common among migraine with aura patients and less common among patients using preventive medication (Quintela et al., 2006).

In one prospective study, the prevalence of postdromal symptoms among migraine patients were 80 % (Quintela et al., 2006). Among the most common postdromal symptoms are tiredness, asthenia, stiff neck, mood change, head discomfort, photophobia, yawning, somnolence and difficulties concentrating (Quintela et al., 2006, Giffin et al., 2016, Kelman, 2006, Bose et al., 2018). One study also indicates similarities between premonitory and postdromal symptoms in the same individual (Karsan et al., 2021). Migraine patients using sleep to treat the migraine headache also experience postdromal symptoms after awakening (Blau, 1982, Karsan et al., 2021).

1.2.3 Migraine chronobiology

Some migraine patients experience different frequency of attacks in different parts of the year, attacks happening at specific times of the week or patterns of attack onset at specific times during the day. Several biological rhythms correspond to similarly timed cycles. One of these is the circadian rhythm with cycles of about 24 hours and function related to sleep and wake (Poulsen et al., 2021). Another cycle strongly connected to migraine is the menstrual cycle where changes in levels of estrogen and possibly progesterone are likely related to the onset of attacks (Poulsen et al., 2021, Cupini et al., 2021, Fox and Davis, 1998).

Most studies report the morning as the most frequent time of migraine attack onset. However, results from studies investigating circadian distribution of migraine onset show great variation and some studies also report an afternoon peak or a biphasic pattern of attack commencement time (Poulsen et al., 2021, Fox and Davis, 1998, Baksa et al., 2019). Thus, chronobiological variation also indicate variation of phenotype within the migraine diagnosis. One study showed that early morning attack onset (00:00 – 06:00) was linked to early chronotypes and early chronotypes were associated with worse sleep quality. Late chronotypes were also associated with later attacks (12:00 – 18:00) (van Oosterhout et al., 2018). Another study found an association between insomnia and morning attack onset

(Alstadhaug et al., 2007). Short sleepers have also displayed increased likelihood of morning headaches on awakening (Kelman and Rains, 2005).

Due to this variation in circadian migraine onset phenotype, we propose that circadian or sleep related subgrouping of migraine patients may be important and represent variations in migraine pathophysiology. Engstrøm et al. defined those usually having migraine attack onset during sleep or upon awakening as sleep related migraine. Those who usually had attack onset during the day before noon, after noon or at no regular onset were defined as non-sleep related migraine (Engstrom et al., 2013a). We employ a similar model to investigate migraine subgroups with different circadian attack onset patterns.

1.3 Migraine pathophysiology

Migraine is likely a disease of neuronal dysexcitability and abnormal brain connectivity with a genetic component, causing altered cortical responsivity and sensory processing. The underlying pathogenesis is still largely unknown. However, the mechanisms of migraine must be able to produce a dynamic and complex brain dysfunction, causing a diverse spectrum of symptoms when cycling through the migraine phases (Cosentino et al., 2014b, Peng and May, 2019, Goadsby et al., 2017, Mykland et al., 2019, Barbanti et al., 2020b, Reducha et al., 2022).

The cyclic nature of the migraine disease has made longitudinal study designs important in attempts to unravel the dynamically changing properties of the migraine brain (Bjørk and Sand, 2008, Schulte and May, 2016, Stankewitz and May, 2009). This concept has led to a dilemma in migraine research: Balancing the need for repeated measurements against the need to compare different subjects due to interindividual differences. On one hand, notable insight into migraine mechanisms have been yielded from studies applying large amounts of measurements in few subjects. The seminal study by Schulte and May strengthened the importance of hypothalamus in migraine attack initiation by recording daily magnetic resonance imaging (MRI) in one migraine subject, over a total of 30 days and 3 complete, spontaneous migraine attacks (Schulte and May, 2016). This approach accounts well for intraindividual variation, but the generalisability to the complete and diverse migraine group may be uncertain. Other studies have applied fewer repeated recordings in larger groups of subjects, such as the important study series into migraine neurophysiology by Sand et al. (Bjork et al., 2011, Sand et al., 2009, Uglem et al., 2017a). However, the migraine diagnosis allows for a heterogenous group of patients. Thus, there is great possibility for the existence of subgroups with different pathophysiological mechanisms within the migraine disease

category. Studies with greater numbers of subjects is necessary for analysis of such subgroups. However, these analyses are often limited to the interictal phase because most migraine patients spend the bulk of their time between attacks (Bjork et al., 2009, Omland et al., 2013). Thus, identifying parameters which differentiate migraine patients with different underlying causes may be essential to interpret migraine research. Attempts at evaluating mechanisms which differ within the complete migraine group without recognising the possibility of distinct subgroups could generate misleading results.

1.3.1 The period leading up to a migraine attack

During the 24-48 hours preceding a migraine headache attack, increased activity of the hypothalamus in response to trigeminal nociceptive stimulation has been observed. This activation occurred in the lateral anterior part of the hypothalamus, where the suprachiasmatic nucleus and other nuclei responsible for circadian rhythm and sleep-wake regulation are located. This area has previously been hypothesised to play a role in migraine attack generation and migraine chronification (Schulte and May, 2016, Denuelle et al., 2007, Schulte et al., 2020a, Schulte and Peng, 2019). Pituitary adenylyl cyclase-activation protein (PACAP), which is a neuropeptide known to trigger migraine attacks (Edvinsson et al., 2018), and glutamate are released into the suprachiasmatic nucleus from direct monosynaptic connection from the retina. Thus, implying a close connection between brain areas related to the preictal phase of migraine and mechanisms synchronising the suprachiasmatic nucleus to the diurnal cycle (Schulte and Peng, 2019).

The suprachiasmatic nucleus also has projections to the paraventricular nucleus of the hypothalamus (PVN) (Hermes et al., 1996). PVN regulates activity of the spinal trigeminal nucleus (Robert et al., 2013) and may therefore be an important connection between sleep, waking, migraine initiation and trigeminal pain. Trigeminal pain perception has been shown to change late in the preictal phase (Uglem et al., 2017a), substantiating the hypothesised preictal role of the PVN. One of the most accepted migraine triggers is stress, which cause increased release of corticotropin-releasing hormone (CRH) produced in the PVN. CRH-release also display circadian rhythmicity with the highest levels of release in the morning. Furthermore, CRH may indirectly influence trigeminal nociception via orexins (Schulte and Peng, 2019). The hypothalamic sleep-wake systems also modulate rostroventral medulla and periaqueductal grey (PAG) which regulate sensory input. Additionally, the hypothalamus regulates other systems related to premonitory symptoms such as appetite and yawning (Schulte and Peng, 2019, Guven et al., 2018). Intrinsic connectivity in several networks and

hypothalamic connectivity to the limbic system appear to increase towards the attack before dropping to baseline levels during the attack (Stankewitz and Schulz, 2022, Stankewitz et al., 2021). Consequently, hypothalamus losing control of the limbic system may be of importance in attacks (Stankewitz et al., 2021).

During preictal resting state imaging, the right nucleus accumbens display altered connectivity to the left amygdala, left hippocampus and left gyrus parahippocampalis. The dorsal rostral pons including dorsal raphe also display increased functional coupling with the nucleus accumbens (Schulte et al., 2020b). Dorsal raphe nucleus may give dopaminergic input to the accumbens shell (Hasue and Shammah-Lagnado, 2002). Extracellular dopamine increase in the shell of nucleus accumbens is seen when inducing yawning in rats by activating oxytocinergic neurons from PVN to the hippocampus and amygdala (Sanna et al., 2012). Yawning is a common premonitory symptom in migraine. Thus, this network appears clinically relevant for mechanisms of migraine pathophysiology occurring before attacks.

Studies on somatosensory evoked potentials in migraine indicate increased thalamocortical drive just prior to the migraine attack. This increased drive may be caused by decreased preictal cortical preactivation due to decreased serotonergic state setting activity. This suggestion is based on the phenomenon of thalamocortical dysrhythmia which may be caused by hypoactivity in state setting subcortico-cortical projections causing hyperpolarisation of the thalamus or due to increased inhibition (Coppola et al., 2007, Bjork et al., 2011, Llinas and Steriade, 2006). Other studies have found increased power of delta, theta and beta bands in the EEG before an attack. Coexistence of slow delta/theta and fast beta oscillations may be caused by thalamocortical dysrhythmia where thalamus produce rhythmic slow oscillations similar to the burst mode usually observed during slow wave sleep. These oscillations generate increased synchronisation of cortical oscillations and cortical disinhibition (Bjork et al., 2011, Llinas et al., 1999). Similar findings of increased baseline beta power accompanied by increased sensorimotor responsivity has also been interpreted as reduced preictal cortical preactivation, possibly due to reduced serotonergic state setting (Mykland et al., 2019, Schoenen, 1996). Furthermore, preictal restoration of facilitatory responses to repetitive transcranial magnetic stimulation (rTMS) may indicate that thresholds for inhibitory homeostatic responses are increased as is expected if cortical activity is reduced (Cosentino et al., 2014c). Interestingly, the lateral hypothalamus also controls serotonergic neurons in the dorsal raphe, theoretically connecting preictally altered hypothalamic function and cortical state setting mechanisms (Celada et al., 2002).

The time leading up to a migraine attack is also likely characterised by increased somatosensory excitability starting in the brainstem and spreading to somatosensory cortex, reaching its maximum on the day before the migraine attack. The inhibitory capability of primary somatosensory cortex may also be lower the day before the attack compared to during the attack (Hsiao et al., 2022). Hyperresponsivity of sensorimotor cortex and visual systems have also been demonstrated during the preictal phase and may be due to decreased intracortical inhibition (Mykland et al., 2019, Sand et al., 2008c).

1.3.2 The migraine headache attack

The hypothalamic activation seen in the preictal phase may persist in the ictal phase (Denuelle et al., 2007). The hypothalamus also display greater functional coupling with the dorsal pons during the ictal phase (Schulte and May, 2016, Schulte et al., 2020b) Furthermore, the rostral pons displays increased activation to trigeminal nociceptive stimuli during the attack (Stankewitz et al., 2011, Schulte and May, 2016). Imbalance between brainstem nuclei during migraine attacks may cause a dysregulation of antinociception and vascular control (Weiller et al., 1995).

It is suggested that the trigeminal nucleus caudalis is activated during the initiation of a migraine attack, causing unilateral activation of the trigeminal ganglion and peripheral release of calcitonin gene-related peptide (CGRP), possibly from C-fibres. CGRP release may cause vasodilatation and activation of Aδ-fibres through increased intracellular levels of cyclic adenosine monophosphate (cAMP). The activated Aδ-fibres signal back to the trigeminus nucleus caudalis and cause sensation of pain (Haanes and Edvinsson, 2019). This mechanism may cause peripheral sensitisation of Aδ-fibres and consequently hyperalgesia and allodynia during the migraine attack. Triptans may also act peripherally reversing the hyperexcitability of Aδ-fibres (Haanes and Edvinsson, 2019). However, recent results indicate that sumatriptan instead reduces central sensitisation without any modulation of peripheral sensitisation. This effect may be dependent on CGRP in the dorsal horn and may act presynaptically on the synapse between primary and secondary sensory neurons. The effect also seems specific to the trigeminal sensory system, possibly because of a larger portion of Aδ-fibers compared to spinal dorsal roots (Peng et al., 2022).

Dopaminergic systems may inhibit trigeminocervical neurons. It is hypothesised that migraine patients suffer from chronic dopaminergic hypofunction leading to upregulation of dopamine receptors. Dopamine release is then hypothesised to increase during attacks, stimulating hypersensitive receptors without capability of stopping trigeminovascular

activation. Dopamine release return to baseline levels after the attack (Barbanti et al., 2013). Contradictory, another study showed dopamine release reduction and imbalance in the striatum during attacks when investigating the D2/D3 receptor system (DaSilva et al., 2017). Consequently, the role of the dopaminergic system in migraine attack generation is likely complex and require further evaluation.

The increased preictal somatosensory excitability normalises to interictal levels during the attack (Hsiao et al., 2022, Mykland et al., 2019). Similar normalisation has been seen for hypothalamic connectivity and widespread intrinsic network connectivity (Stankewitz et al., 2021, Stankewitz and Schulz, 2022), and for thalamocortical activation and cortical responsiveness (Coppola et al., 2007, Coppola et al., 2005). However, cortical preactivation levels is suggested to increase during the attack (Coppola et al., 2007). This is in line with the observation that migraine subjects have shown reduced responses during trains of rTMS ictally, as thresholds for inhibitory homeostatic responses may be reduced due to increased ictal cortical preactivation (Cosentino et al., 2014c).

1.3.3 The period following a migraine attack

Less is known about the phase following resolution of migraine headache than the other phases of the migraine cycle. The postictal phase is usually defined as lasting up to 24 hours after attack cessation based on the reported duration of postdromal symptoms (Peng and May, 2020). Blau have suggested that the whole brain may be involved in the aftermath of attacks due to the range of symptoms described (Blau, 1991). Indications of a widespread brain affection has been found when comparing cerebral blood flow in the postictal and preictal phase, where the postictal phase was characterised by a global blood flow reduction (Bose et al., 2017). Other studies have not shown any difference between the interictal and postictal phase in sensorimotor processing or resting state EEG power (Mykland et al., 2019, Bjørk and Sand, 2008).

However, there are other indications of altered central nervous function in the postictal phase. In a study with repeated measurements in one patient, the visual cortex displayed increased activity in response to trigeminal pain compared to during attacks (Schulte and May, 2016). Similar multisensory integration of trigeminal pain and visual cortex light response is also known to exist in interictal migraine subjects (Boulloche et al., 2010). Brainstem function may also be affected during the first three days following an attack, shown as prolonged brainstem auditory-evoked potentials interpeak latency (Sand et al., 2008b). A negative correlation between days elapsed since migraine attack cessation and somatosensory cortical

lateral inhibition has also been observed (Coppola et al., 2016). However, much remain to be explained regarding mechanisms of the period following migraine attacks and the cause of postdromal symptoms.

1.3.4 Between migraine attacks

The neurophysiology of the interictal migraine brain has been widely examined over the past decades. A caveat in the interpretation of available studies has been the partly conflicting results. First, migraine patients do not respond with normal potentiation to high frequency rTMS. This finding may indicate an interictal glutamatergic dysfunction (Cosentino et al., 2014c). However, other interictal findings point toward dysfunctional inhibition. Lateral inhibition and thalamocortical activity measured by somatosensory evoked potentials were reduced interictally (Coppola et al., 2016). Abnormal inhibitory responses to high frequency rTMS also indicate lower threshold for inducing inhibitory mechanisms in the interictal phase (Cosentino et al., 2014a). Magnetic resonance spectroscopy has also revealed abnormalities of both glutamate and gamma-aminobutyric acid (GABA) levels (Younis et al., 2017, Aguila et al., 2015), and GABA levels correlated with central sensitisation scores (Aguila et al., 2016). A unifying hypothesis may include interictal cortical hyperresponsivity with decreased thresholds for inhibitory homeostatic responses. This hypothesis can explain findings which a hypothesis of reduced cortical preactivation cannot (Cosentino et al., 2014b). However, some authors argue that reduced cortical preactivation may exist in the interictal phase, supported by findings of the ability of rTMS to increase thalamocortical drive in migraine patients but not in controls (Coppola et al., 2005, Coppola et al., 2013). It is likely that some conflicting findings is a result of heterogeneity within the migraine diagnosis and differences in underlying pathophysiology (Cosentino et al., 2014b).

Lack of habituation have been suggested to be a consistent finding in migraine patients during examinations of responses in different sensory modalities. Reduced cortical preactivation due to altered thalamocortical loop activity and aminergic state setting was originally suggested to explain these findings as part of the *ceiling theory*. This theory suggests that low preactivation levels cause a large range for suprathreshold activation up to a limit where habituation begins. The theory also attempts to explain reduced first block amplitude in such recordings (Coppola et al., 2009, Coppola et al., 2005, Schoenen, 1996). However, other findings supporting reduced first block amplitudes of visual evoked potentials in interictal migraine patients are very limited or non-existing (Omland et al., 2013). Recent blinded examinations of visual evoked potentials habituation do also not

support the theory of lack of habituation in migraine patients (Omland et al., 2016). Similarly, habituation deficits of pain related laser evoked potentials have not been confirmed in a recent blinded study (Uglem et al., 2017b). However, lack of habituation in other sensory modalities may be an occurring phenomenon and may also represent a common finding of several diseases including migraine (Omland et al., 2016, de Tommaso et al., 2014, Brighina et al., 2016).

Dysfunctional thalamocortical loops have been suggested to cause reduced cortical inhibition in interictal migraine patients. This interpretation was made based on examinations of cortical silent period (CSP) (Curra et al., 2007, Maier et al., 2011). Shorter CSP duration has also been reported for interictal migraine by others (Khedr et al., 2006), in the subgroups of migraine with aura (Aurora et al., 1999), in female migraine patients (Neverdahl et al., 2017) and in preovulatory recordings (Yuksel and Topalkara, 2021). However, other studies did not confirm these findings (Afra et al., 1998, Werhahn et al., 2000, Siniatchkin et al., 2007, Siniatchkin et al., 2009, Gunaydin et al., 2006).

Migraine subjects display interictal hypometabolism in pain processing brain regions including somatosensory cortex. PAG and other areas of nociceptive and sensory processing do also have stronger connectivity in migraine subjects. Both the hypometabolism of central pain matrix and pain processing connectivity was correlated with migraine frequency (Kim et al., 2010, Mainero et al., 2011). The secondary somatosensory cortex of interictal migraine patients also displays unexpected responses during high frequency rTMS stimulation. Stimulation-induced hypoalgesia occuring in controls but not in migraine patients suggest reduced intracortical inhibition in migraine (Uglem et al., 2016). Furthermore, luminous stimulation activates visual cortex in migraine patients, but not in controls, and is potentiated by trigeminal pain. These results indicate cortical hyperexcitability in migraine and multisensory integration (Boulloche et al., 2010). On the other hand, spinal trigeminal nuclei display lower activation to trigeminal nociceptive stimuli outside of attacks compared to controls (Stankewitz et al., 2011). These results indicate that evaluation of cortical inhibition and excitability in migraine should be interpreted with respect to possible dysfunction of subcortical structures.

1.3.5 Migraine with and without aura

In 1958, Milner suggested that the spreading depression of Leão might be the neural correlate of migraine aura. He made this suggestion based on the similarity between the propagation rate of about 3 mm per minute of aura scotomas described by Lashley in 1941 and the

description of the spreading depression inhibition wave to be about 3 mm per minute by Leão in 1944 (Milner, 1958, Leao, 1944). In 1945 Engel et al. had already observed a transient focus of slow-wave abnormalities with EEG during visual aura with homonymous hemianopia in three migraine subjects. These findings were not reproduced by Dow et al. in six cases of visual aura in 1947 (Dow and Whitty, 1947). However, in 2001, Bowyer et al. applied magnetoencephalography (MEG) during aura in 4 migraine patients. They observed direct current (DC) MEG field shifts during spontaneous and visually induced aura and suggested that these observations resemble what is reported during cortical spreading depression (CSD) in animal models (Bowyer et al., 2005). Similar findings of suppressed cortical activity and field changes had also been reported previously during migraine headache. These studies also observed large amplitude waves of several seconds duration which has not been described previously in spreading depression and which Bowyer et al. did not reproduce (Barkley et al., 1990a, Barkley et al., 1990b, Bowyer et al., 2005). CSD is by many considered the cause of migraine aura. However, several issues remain in translating CSD to migraine aura. These issues include reports of bilateral aura symptoms, while CSD should propagate within the same hemisphere. Concurrent visual and somatosensory aura and the evolvement of visual aura into somatosensory aura is also difficult to explain with CSD, partly due to travel distance across the cerebral cortex, unless multifocal CSDs are hypothesised to occur. There is also uncertainty regarding whether CSD may initiate migraine attacks, and it is known that MEG DC shifts also happen during other tasks and stimuli. Additionally, CSD being the underlying cause of migraine without aura is by many considered unlikely due to lacking evidence. There is also a possibility that spreading depression occur in other structures such as the thalamic reticular nucleus and not just the cerebral cortex alone (Bolay et al., 2019, Vgontzas and Burch, 2018, Tepe et al., 2015). Furthermore, Hall et al. used MEG to investigate cortical oscillations during visual aura with scintillating scotoma in one patient who did not have a subsequent headache attack. They observed alpha band desynchronization in left extrastriate and temporal cortex in the time corresponding to the aura (Hall et al., 2004). Some results also suggest suppression of visual and somatosensory evoked potentials during aura (Coppola et al., 2019).

Altered neurophysiological measurements are more frequently present and of greater amplitude in migraine patients with aura than without aura. However, most neurophysiological abnormalities are shared between the two groups. Contradictory to the lack of habituation described for some sensory modalities in the general migraine group,

subjects with familial hemiplegic migraine (FHM) have displayed increased visual evoked potentials habituation (Coppola et al., 2019).

Rare genetic variants of migraine in form of FHM have provided insight into migraine pathophysiology through distinct mechanisms discovered in these migraine subtypes. Mutations in the CACNA1A, ATP1A2 and SCNA1A genes cause FHM1, FHM2 and FHM3, respectively. FHM1 is caused by gain-of-function in the $Ca_V2.1$ channel leading to increased neurotransmitter release. FHM2 is caused by loss-of-function in Na^+/K^+ ATPase responsible for astrocytic glutamate clearance. FHM3 is caused by either gain- or loss-of-function in $Na_V1.1$ channels probably leading to increased frequency of neuronal firing in addition to increase of neuronal excitability and neurotransmitter release (Pietrobon, 2007, Uchitel et al., 2014, Vecchia and Pietrobon, 2012). Some also argue that PRRT2 should be included as the fourth autosomal dominant gene causing FHM. Variations of PRRT2 also cause hypersomnia (Riant et al., 2022).

1.3.6 Migraine genetics

Twin-studies have indicated an estimate heritability of about 50 % in migraine with about 1.4-3.0 times increased risk in first degree relatives (Fitzgerald et al., 2021, Russell et al., 1995, Ulrich et al., 1999, Ziegler et al., 1998). The most recent genome-wide association study in migraine identified 123 risk loci for migraine. Some genetic risk variants differed between migraine patients with and without aura. However, most variants increased the risk of migraine with no regard to aura-related subtype. Tissue enrichment analyses indicated a role of both vascular and central nervous tissue in migraine pathophysiology. However, no indication of consistent change in risk of coronary artery disease or hypertension was found. Enrichment in the CNS was found for the nucleus caudatus of the dorsal striatum. One locus also contained the genes encoding for CGRP (Hautakangas et al., 2022).

1.4 The connection between migraine and sleep

The close connection between migraine and sleep has been known for centuries. Descriptions of this interplay include observations of a treatment effect of sleep during attacks and a tendency for attacks to follow disturbed or insufficient sleep. More recent studies have also confirmed these observations (Blau, 1982). Migraine patients do in general report worse subjective sleep quality than healthy controls (Stanyer et al., 2021). About 50 % of migraine patients report that sleep disturbances trigger migraine attacks and 71 % have reported headache attacks awakening them from sleep. A majority of migraine subjects also report that they utilise sleep as a palliative agent for headache attacks. About 85 % stated that they chose

to sleep because of headache occasionally and 75 % stated that they were forced to sleep due to headache at least occasionally. Difficulty initiating and maintaining sleep are common in migraine subjects and the incidence of insomnia-like sleep patterns of shortened sleep are at least three times higher in migraine patients than in the general population (Kelman and Rains, 2005). Migraine is also more common among people with insomnia (Kim et al., 2018). This bidirectional risk-relationship between migraine and insomnia was demonstrated in the large epidemiological HUNT studies (Odegard et al., 2011, Odegard et al., 2013). Another study found three times increased likelihood of excessive daytime sleepiness among migraine patients and five times increased likelihood of severe sleep disturbances (Odegard et al., 2010). The prevalence of disordered sleep also appears to be similar between migraine patients with and without aura (Lateef et al., 2011).

Polysomnography recordings have indicated shorter rapid eye movement (REM) sleep in migraine patients (Stanyer et al., 2021). Decreased REM density has also been observed in sleep preceding a migraine attack (Goder et al., 2001, Lucidi et al., 1996). This finding was accompanied by decreased number of arousals and decreased beta power during slow wave sleep. Authors interpreted this result as increased need for sleep in nights preceding migraine attacks because REM density previously have been shown to decrease with reduced prior sleep duration. They also suggested that decreased cortical activation preceding a migraine attack, due to changes in aminergic nuclei function or impaired cerebral cholinergic input, may explain the findings (Goder et al., 2001, Lucidi et al., 1996). One study reported that an attack was more likely two days after sleep fragmentation (Bertisch et al., 2020). Another study of migraine occurring at night suggested that migraine start from REM sleep (Dexter and Weitzman, 1970). This group also later suggested an association between increased slow wave sleep and REM sleep, and migraine occurring in the morning (Dexter, 1979). However, studies of sleep architecture in migraine patients have provided diverging results. Yet, some suggest that decreased arousability the night before migraine may be a consistent finding (Brennan and Charles, 2009).

Engstrøm et al. showed more awakenings and slow wave sleep in interictal migraine patients compared to controls. Slow wave sleep, and possibly increased sleep pressure, were also correlated with lower pain thresholds in migraine patients. In subgroup analyses, more awakenings pertained to sleep related migraine and more slow wave sleep to non-sleep related migraine (Engstrom et al., 2013b, Engstrom et al., 2013a).

Interestingly, sleep immediately after migraine attacks is similar to sleep during headache free intervals, and is not associated with shorter duration, higher disruption or worse quality of sleep (Vgontzas et al., 2020). However, reporting poor sleep was associated with a higher rate of headache during the following 6 weeks in migraine patients. This association was especially seen for patients with coexisting moderate to high stress levels (Vgontzas et al., 2021).

Several brain regions and molecular systems that likely take part in migraine pathophysiology also take part in sleep physiology. Among these are the hypothalamus with recently strong implications in migraine pathophysiology and an important role in sleep-wake regulation (Vgontzas and Pavlovic, 2018). Dorsal raphe which may regulate cortical activation is also important in the initiation of REM sleep which have been found by some to be altered in migraine patients and related to attack onset. Dopamine is also involved in several premonitory migraine symptoms such as yawning and is also an important transmitter in the system promoting arousal via hypothalamic input to the PAG. An increased risk for restless legs in migraine patients is also interesting in this context as restless legs is thought to involve a dysfunction of descending dopaminergic systems from hypothalamus to the spinal cord (Vgontzas and Pavlovic, 2018, Tiseo et al., 2020, Saper et al., 2005). Shared alterations of functional connectivity in default mode network subnetworks between migraine and insomnia have also been shown (Chou et al., 2021).

Genome-wide genetic correlation analyses have revealed several sleep traits with genetic overlap with migraine. Of these, the strongest correlation was found for insomnia symptoms. Other overlapping traits were difficulty awakening, short and long sleep duration, and daytime sleepiness (Daghlas et al., 2020).

1.4.1 Sleep related migraine subgroups

The close connection between sleep and migraine indicate that the chronobiology of migraine subjects is a necessary pathway to explore. Studies of migraine chronobiology have identified different circadian peaks of migraine attack onset. Migraine attacks appear to congregate during night-time/in the early morning or during the afternoon (Poulsen et al., 2021). These observations indicate the relevance of ongoing sleep for some attacks and possibly previous sleep for other attacks. The findings also convey the possibility of circadian subgroups of migraine patients. As described previously, Engstrøm et al. have defined one subgroup of migraine patients to be sleep related with attacks occurring during sleep or at awakening and another subgroup to be non-sleep related (Engstrom et al., 2013a, Engstrom et al., 2014).

They discovered signs of disturbed sleep in the sleep related migraine group compared to controls. Sleep related migraine patients had reduced slow wave sleep, increased number of awakenings and had fewer K-bursts and D-bursts which may represent the ability to get slow wave sleep. This group of migraine subjects may therefore have a reduced ability to achieve sufficient slow wave sleep and consequently increased arousability. Subjects with non-sleep related migraine had increased daytime tiredness and more slow wave sleep. They also had fewer fast arousals and higher K-burst index. This group may therefore be relatively sleep deprived and have an increased need for sleep. An alternative hypothesis for these findings is hypoarousability of non-sleep related migraine subjects (Engstrom et al., 2013a, Engstrom et al., 2014). Grouping migraine patients by different circadian attack onset have also revealed differences in interictal brain responses measured with functional MRI (fMRI) (Baksa et al., 2022).

1.5 Sleep restriction

Sleep deprivation induce changes in inhibitory and excitatory systems in healthy subjects (Salehinejad et al., 2022). Sleep deprivation in rats do also induce changes in the expression of metabotropic glutamate receptors and GABA-B receptors (Tadavarty et al., 2011), and increase membrane GABA-A receptors, possibly as homeostatic mechanisms to stabilise excitability related to circadian plasticity changes (del Cid-Pellitero et al., 2017). Restricting sleep to about 50 % for two nights is a human model for insufficient sleep. Applying this model of sleep restriction increase pain-elicited EEG responses and reduce somatosensory cortex processing (Matre et al., 2015). Sleep restriction also increase pain sensitivity in healthy subjects (Matre et al., 2015). Increased pain sensitivity is seen in migraine patients (Uglem et al., 2017a, Sand et al., 2008a, Burstein et al., 2000), and may be related to increased sleep need (Engstrom et al., 2013b) and reduced intracortical inhibition (Uglem et al., 2016). Thus, investigating effects of sleep restriction on the central nervous system in migraine patients is relevant to unravel migraine and sleep specific pathophysiology.

1.6 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has been widely used to stimulate the human cortex since Barker et al. published the first report of this technique in 1985. They used a circular magnetic coil placed over the scalp in a position corresponding to the motor cortex and recorded motor evoked potentials (MEP) in the contralateral abductor digiti minimi muscle as a response to the cortical magnetic stimulation (Barker et al., 1985). This technique is performed by sending a brief electric pulse through a coil of wires. A magnetic field is then

induced with flux perpendicular to the plane of the coil wiring. This in turn induces an electric field perpendicular to the magnetic field in the targeted area of the brain. This electric field may excite neurons directly or through induced current from the changing electrical field. Several types of coil designs are available, and these induces magnetic fields with different properties. A figure-of-eight coil is often used to produce a more focal stimulation than a circular coil (Hallett, 2007). Current guidelines for the use of TMS is presented by the International Federation of Clinical Neurophysiology (IFCN) (Rossini et al., 2015).

Performing TMS on the motor cortex can elicit MEPs in corresponding muscles, which can be recorded with surface electromyography (EMG) electrodes. The neural population responsible for eliciting this response is not fully delineated. Recording signals at the level of the high cervical cord in response to TMS have revealed several waves corresponding to a single MEP. The first volley recorded is termed the direct wave (D-wave) and is similar to waves observed from transcranial electrical stimulation. Several later indirect waves (I-waves) follow the D-wave. These occur at interpeak intervals of about 1.5 ms. It is suggested that the D-wave is elicited from direct activation of axons from corticospinal cells in layer 5 of the cortex. The first I wave (I1-wave) is thought to be caused by activation of axons from layer 2/3 pyramidal cells to layer 5 pyramidal cells presynaptically. Furthermore, the later I-waves are proposed to be caused by activation of other axons in the interconnections between these pyramidal cells and cortical GABAergic interneurons (Day et al., 1989, Di Lazzaro et al., 1998, Di Lazzaro et al., 2008, Di Lazzaro et al., 2012).

Different TMS parameters can be applied to elicit responses which are dependent on different parts of the brain inhibitory/excitatory system, neural plasticity and cerebral states. Single test stimuli (TS) may be utilised to record the peak-to-peak amplitude of MEPs or to induce inhibitory effects on an already activated muscle. A conditioning stimulus (CS) may be elicited preceding the main TS to activate and evaluate several intracortical circuits with facilitatory and inhibitory effects. This category of techniques is labelled as paired pulse TMS (ppTMS). To induce lasting, modulatory effects on cortical excitability, one may utilise several techniques composed of repeated stimuli such as rTMS. Evaluating effects of peripheral stimulation on the cortically activated MEP is also a useful method (Rossini et al., 2015).

1.6.1 Cortical silent period (CSP)

When performing TMS over motor cortex during applied isometric muscle contraction, one elicits a phenomenon causing sudden resolution of voluntary muscle activation. This effect is

the CSP (Figure 1). The duration of this silent period is dependent on different inhibitory mechanisms, which are not completely understood. The early part of CSP (the first 50-75 ms) may depend on spinal inhibition (Ziemann et al., 2015). Reduced excitability of spinal motor neurons, presumably caused by reduced cortical drive, was first suggested to cause the spinal effects on CSP (Fuhr et al., 1991). Other observations have indicated Renshaw cell inhibition or motoneuron afterhyperpolarization as possible spinal mechanisms contributing to the CSP (Ziemann et al., 1993). The later parts of the CSP likely depend on cortical components. GABA-B receptor mediated inhibition may be the causing mechanism as inhibitory post-synaptic potentials from these receptors gave similar duration of inhibition of pyramidal cells in animals and because the duration increased with stimulation intensity (Nakamura et al., 1997). While some studies did not support this hypothesis, the CSP is now considered to be mediated by GABAergic mechanisms, where GABA-B receptors constitute the main mediator. However, CSP following low intensity stimulation and short CSP duration appear to also be dependent on GABA-A receptors which increase the silent period. CSP after high intensity stimulation and longer CSP durations also seem to be dependent on GABA-B receptor inhibitory post synaptic potential suppression. These post synaptic potentials are suppressed by presynaptic GABA-A receptors, possibly by increasing intracellular Cl- which blocks GABA-B receptor associated K+ channels (Ziemann et al., 2015, Hupfeld et al., 2020, Zeugin and Ionta, 2021, Kimiskidis et al., 2006).

Furthermore, dopamine also lengthens the duration of CSP, presumably by enhancing post-synaptic GABA sensitivity (Priori et al., 1994, Ziemann et al., 2015, Hupfeld et al., 2020, Ziemann et al., 1996) This was shown in pharmaco-TMS studies using the D1 and D2 receptor agonist pergolide mesylate in healthy subjects (Ziemann et al., 1996) and levodopa in Parkinson's disease (Priori et al., 1994). Cabergoline which act mainly on D2/D3 receptors did not alter CSP duration (Korchounov et al., 2007). Experiments in striatal slices also show increased GABA release in striatum due to D1 receptor activation and reduced GABA release due to D2 receptor activation (Harsing and Zigmond, 1997). Thus, one may speculate if the dopaminergic effect on CSP is due to D1 receptor mediated mechanisms. Furthermore, the dopaminergic effects on CSP have been interpreted to be working mainly at the level of basal ganglia. Priori et al. showed that dopaminergic drugs and anticholinergics are likely to increase CSP duration by acting on the subcortical-cortical loops in Parkinson patients. This effect on CSP possibly occur by increasing nigrostriatal dopamine and blocking activity of striatal cholinergic interneurons, but dopaminergic projections from midbrain ventral

tegmentum to the cortex may be an alternative mechanism. In healthy subjects they argued that dopaminergic systems outside of the striatum affect the CSP as levodopa modifies CSP without affecting mobility (Priori, Berardelli et al. 1994). A recent review has also highlighted a possible involvement of the hyperdirect pathway for motor control and its culminating inhibitory effect on thalamus as a possible important mechanism for at least the late part of the CSP (Zeugin and Ionta 2021).

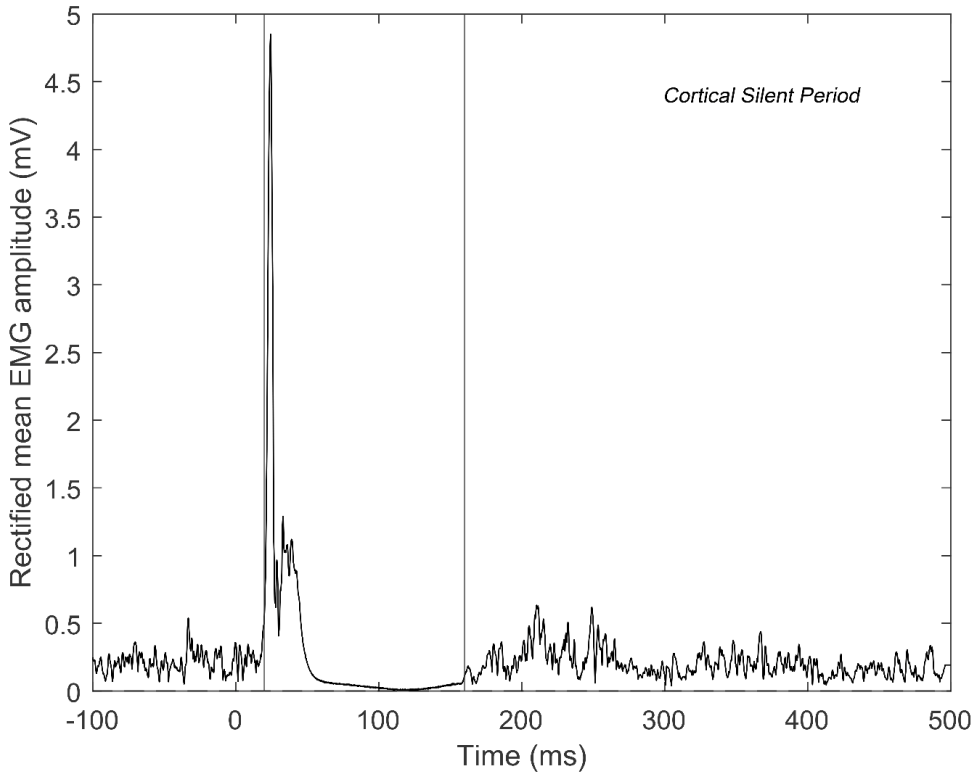

Figure 1 Cortical silent period (CSP) illustration

Rectified mean electromyography (EMG) amplitude in millivolts (mV) during time in milliseconds (ms) for one session of cortical silent period (CSP). TMS was elicited at time 0 ms. Vertical solid lines indicate the CSP onset and offset. The increase in amplitude in the initial part of the CSP measurement is the motor evoked potential (MEP).

1.6.2 Paired pulse transcranial magnetic stimulation (ppTMS)

By combining two magnetic stimulations with different intensity and inter stimulus intervals (ISI), one may measure different excitatory and inhibitory mechanisms via the ppTMS technique (Figure 2). Two types of ppTMS are examined using one CS below the threshold

for eliciting MEP, i.e., the resting motor threshold (RMT), followed by a suprathreshold TS after a given ISI. If the ISI is between 1 and 5 ms, an inhibitory effect named short interval intracortical inhibition (SICI) can be measured. Using ISIs between 7 and 20 ms, one may measure the facilitatory intracortical facilitation (ICF) effect. SICI is thought to represent post synaptic inhibition from α2 and α3 subunits of GABA-A receptors and is controlled by presynaptic GABA-B receptor inhibition (Ziemann et al., 2015, Florian et al., 2008). The CS during SICI also appear to suppress late I-waves while the I1-wave is unaffected (Di Lazzaro and Ziemann, 2013). ICF represent a net facilitatory effect, likely as a balance between excitatory N-methyl-D-aspartate (NMDA) receptor activation and the inhibitory GABA-A receptor mediated inhibition represented in SICI (Ziemann et al., 2015). ICF does not produce significant change in any I-waves, possibly suggesting that ICF may be dependent on long-range connections such as those from premotor cortex (Di Lazzaro and Ziemann, 2013). The D2/D3 receptor agonists cabergoline which had no effect on CSP, appear shift both ICF and SICI towards a larger inhibitory component. This effect may be caused by dopamine terminals which synapse directly onto parvalbumin positive large basket cells and chandelier cells which are inhibitory interneurons. Dopamine terminals may also depress excitatory synaptic transmission between horizontal connections of pyramidal cells as dopamine terminals are directly connected to the dendrites of these cells (Korchounov et al., 2007). The inhibitory effect measured as SICI is increased by the D1/D2 receptor agonist pergolide mesylate and bromocriptine which is a strong D2 agonist and a partial antagonist or agonist of D1. On the other hand, the dopamine D2 receptor antagonist haloperidol decreases SICI (Ziemann et al., 1997). Thus, the D2 receptor may play an important role in regulating SICI and ICF. SICI have in several studies been found to be decreased after sleep deprivation (Civardi et al., 2001, Scalise et al., 2006, Kreuzer et al., 2011, Placidi et al., 2013, Salehinejad et al., 2022). This reduction may be associated with a lack of sufficient desaturation of synaptic potentiation and compromised learning, memory, and attention (Salehinejad et al., 2022).

Using a longer ISI of about 50-200 ms and a suprathreshold CS, one may elicit the inhibitory effect termed long interval intracortical inhibition (LICI). This effect is suggested to represent GABA-B mediated slow inhibitory post synaptic potentials. This effect is also dependent on the availability of GABA in the synaptic cleft, making presynaptic GABA-B mediated regulation of available GABA relevant for the effect (Benwell et al., 2007, Ziemann et al., 2015, McDonnell et al., 2006). Although both CSP and LICI is mainly mediated via GABA-

B receptors, the LICI effect may represent magnitude of inhibition to a greater extent while CSP represent duration (McDonnell et al., 2006). CSP also require higher levels of GABA available before the effect is completely saturated (Benwell et al., 2007). Both LICI and CSP appear to decrease during the day and is possibly related to CRH released from the PVN of hypothalamus. It is also known that CRH modulate GABAergic neurons postsynaptically in the central nervous system (Lang et al., 2011). Similar to SICI, LICI also modulate later I-waves without affecting the I1-wave (Di Lazzaro and Ziemann, 2013).

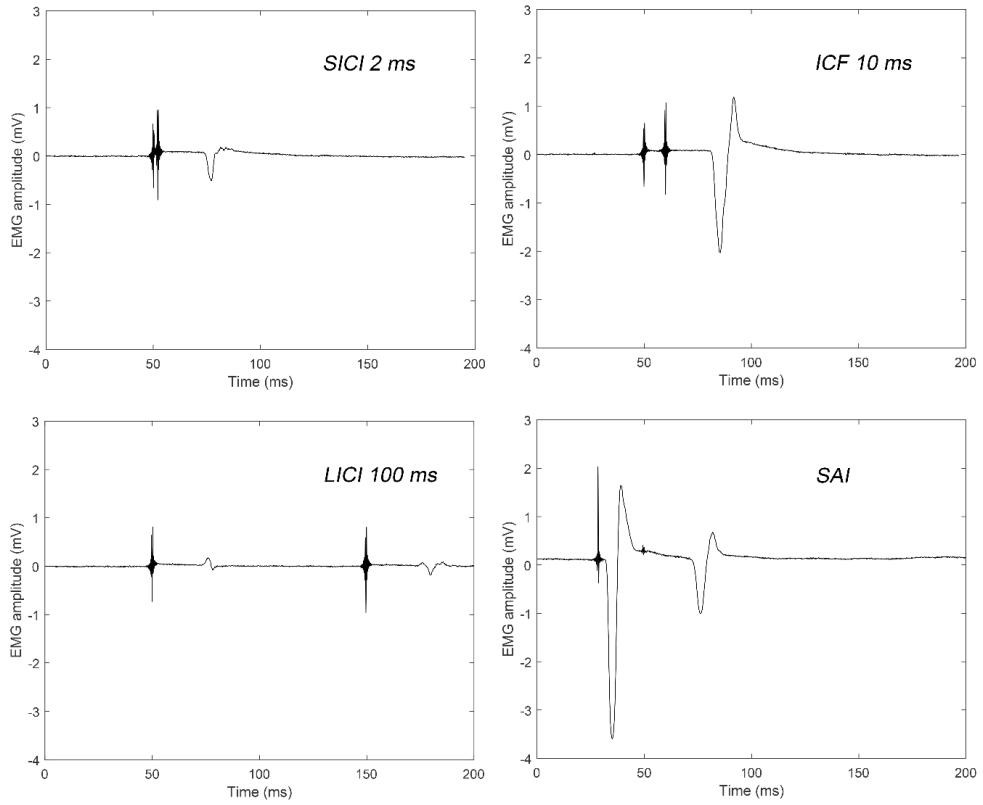

Figure 2 Paired pulse transcranial magnetic stimulation (ppTMS) illustration

Electromyography (EMG) amplitude (mV) from single recordings of short interval intracortical inhibition (SICI), intracortical facilitation (ICF), long interval intracortical inhibition (LICI) and short latency afferent inhibition (SAI) by use of transcranial magnetic stimulation (TMS). The initial stimulus artefacts are caused by the magnetic pulse during the conditioning stimulus (CS) and the following test stimulus (TS). The artefact is followed by a change in amplitude which represent the motor evoked potential (MEP). For SICI and ICF a CS of 80 % resting motor threshold (RMT) and a TS of 120 % RMT were used. For LICI a CS of 109 % RMT and a TS of 120 % RMT were used. For

SAI a CS of median nerve stimulation and a TS of 120 % RMT were used. The interstimulus interval (ISI) represent the interval between CS and TS and is illustrated for 2 ms ISI in SICI, 10 ms ISI in ICF, 100 ms ISI in LICI and 21 ms ISI in SAI.

1.6.3 Short latency afferent inhibition (SAI)

Combining TMS of the motor cortex and peripheral nerve conditioning stimulation may elicit an inhibitory response termed short latency afferent inhibition (SAI) (Figure 2). SAI occur between 1 and 8 ms after the N20 component of somatosensory evoked potentials. Several nerve-muscle combinations can be used to induce this response. Among the most used, are median nerve stimulation combined with EMG recording of the abductor pollicis brevis (APB) muscle and stimulation of the corresponding motor cortex. The SAI effect is not fully understood but is likely mediated both by α1 subunits of GABA-A receptors and cholinergic input from paramedian thalamic nuclei to the primary motor cortex. This effect may occur from cholinergic modulation of basket cells which perform inhibitory shunting on pyramidal neurons. Recruitment of inhibitory interneurons in primary motor cortex via projections from primary somatosensory cortex may also contribute to the response. SAI also suppress late I-waves without affecting the I1-wave but represent inhibitory circuits different from SICI (Ziemann et al., 2015, Turco et al., 2018, Tokimura et al., 2000, Di Lazzaro and Ziemann, 2013).

1.6.4 TMS in migraine patients

Several TMS-measures have previously been investigated in migraine subjects without taking into account circadian timing of examinations or foregoing sleep amount. As described in section 1.3.4, the results of CSP recordings have been inconsistent. It is not known whether time of day for examinations may have varied between groups in these studies, which could account for some inconsistencies (Lang et al., 2011) (Table 1). However, positive studies have indicated reduced CSP in interictal migraine patients (Table 1). Some studies have also found increased interictal ICF (Cosentino et al., 2018, Siniatchkin et al., 2007) and reduced interictal SICI (Brighina et al., 2005, Neverdahl et al., 2017, Brighina et al., 2010), while other studies have failed to confirm these results (Cosentino et al., 2018, Brighina et al., 2005, Afra et al., 1998, Werhahn et al., 2000) (Table 2). Interictal differences in LICI have not been found (Cosentino et al., 2018, Siniatchkin et al., 2007) (Table 2). ICF was also decreased in preictal migraine patients in one study (Neverdahl et al., 2017) (Table 2). One study of SAI found no differences between interictal migraine patients and controls, but instead reduced SAI in the preictal and ictal phase compared to controls (Alaydin et al., 2019)

(Table 3). Another study of SAI found different slope over 5 different ISI between healthy controls and migraine patients, interpreted by the authors as reduced SAI between attacks and increased SAI during attacks (Coppola et al., 2020) (Table 3).

Table 1 Previous studies of cortical silent period (CSP) in migraine patients

Study	Results	Subjects (n)	Coil type	Target muscle	Contraction force	Stimulation intensity	Blinding	Time of examination
(Afra et al., 1998)	No interictal difference between groups	CO: 27 MwoA: 33 MA: 25	Circular	FDI	80 % MVC	110 % RMT	No	Unknown
(Aurora et al., 1999)	Shorter CSP in MA for 100 % RMT, inverse correlation with headache frequency	CO: 9 MA: 9	Circular	FDI	20 % MVC	100 % and 150 % RMT	No	Unknown
(Conte et al., 2010)[1]	No interictal difference between groups	CO: 19 MwoA: 18 MA: 19	Figure-of-eight	FDI	30 % MVC	120 % RMT	No	Unknown
(Curra et al., 2007)	Shorter interictal facial CSP in MIG	CO: 15 MwoA: 15 MA: 11	Circular	Perioral	Maximal	Highest tolerable	TMS	Unknown
(Gunaydin et al., 2006)[2]	No interictal difference between groups	CO: 31 MwoA 15 MA: 15	Circular	ADM	30 % MVC	100 % MSO	TMS	Assumed similar time of day (blinded)
(Khedr et al., 2006)	Shorter interictal CSP in MIG, shorter on migrainous side	CO: 20 MwoA: 10 MA: 18	Figure-of-eight	ADM	Maximal	125 % RMT	No	Unknown
(Maier et al., 2011)	Shorter interictal CSP in MA	CO: 18 MwoA: 15 MA: 15	Circular	FDI	20 % MVC	100 %, 115 % and 130 % RMT	No	Unknown
(Neverdahl et al., 2017)	Shorter CSP in female interictal MIG	CO: 33 (27 female) MIG: 27 (24 female)	Figure-of-eight	APB	50 % MVC	120 % RMT	TMS and analyses	Similar time of day (blinded)
(Ozturk et al., 2002)	Longer CSP in CM	CO: 20 MwoA: 20 CM: 20	Circular	FDI	Maximal	150 % RMT	Analyses	Unknown

(Siniatchkin et al., 2007)	No interictal difference between groups	CO: 15 (female) MwoA: 16 (female)	Figure-of-eight	ADM	20 % MVC	110 %, 120 %, 130 % and 140 % AMT	No	Most recordings in the late morning
(Siniatchkin et al., 2009)	No difference between groups for any phase	CO: 10[3] MwoA: 15[3]	Figure-of-eight	APB	20 % MVC	110 %, 130 % and 150 % RMT	No	Unknown
(Valente et al., 2021)	No difference between groups	EM: 11 CM: 11	Figure-of-eight	FDI	N/A	N/A	No	Unknown
(Werhahn et al., 2000)	No interictal difference between groups	CO: 17 MA: 12 FHM: 9	Figure-of-eight	FDI	30 % MVC	130 % RMT	No	Unknown
(Yuksel and Topalkara, 2021)	Shorter interictal CSP in MwoA and MA	CO: 30 (female) MwoA: 20 (female) MA: 20 (female)	Circular	FDI	20 % MVC	110 % RMT	No	Unknown

CO = Controls; MwoA = Migraine without aura; MA = Migraine with aura; MIG = Migraine; EM = Episodic migraine; CM = Chronic migraine; FHM = Familial hemiplegic migraine; FDI = First dorsal interosseus muscle; ADM = Abductor digiti minimi muscle; APB = Abductor pollicis brevis muscle; MVC = Maximum voluntary contraction; RMT = Resting motor threshold; AMT = Active motor threshold; MSO = Maximum stimulator output

[1]The authors compared the first CSP response in a train of 5 hz rTMS. We do not report the CSP results during rTMS.

[2]The shortest out of 6 CSP duration values were used for analyses.

[3]Children and adolescents.

Table 2 Previous studies of paired pulse transcranial magnetic stimulation (ppTMS) in migraine patients

Study	Results	Subjects (n)	Coil type	Target muscle	Interstimulus interval (ms)	Stimulation intensity	Blinding	Time of examination
(Afra et al., 1998)	No interictal difference between groups	CO: 27 MwoA: 33 MA: 25	Circular	FDI	1-10, 12, 15, 17, 20	CS 97-98 % RMT TS 110 % RMT	No	Unknown
(Brighina et al., 2005)[1]	Reduced SICI in interictal MA	CO: 8 MA: 9	Figure-of-eight	APB	2, 10	CS 80 % RMT TS 120 % RMT	No	Unknown
(Brighina et al., 2010)	Reduced SICI in interictal MA	CO: 9 MA: 9	Figure-of-eight	APB	2, 10	CS 80 % RMT TS 120 % RMT	No	Unknown
(Conforto et al., 2012)[2]	No interictal difference between groups	CO: 9 (female) EM: 10 (female) CM: 7 (female	Figure-of-eight	APB	2	CS 80 % RMT TS 0.5-1 mV MEP	No	Unknown
(Cosentino et al., 2018)	Increased ICF in interictal MwoA for TS 110 % RMT	CO: 24 MwoA: 24	Figure-of-eight	APB	2, 10, 100	SICI/ICF CS 80 % RMT LICI CS 130 % RMT TS 110 %, 130 % and 150 % RMT	No	Unknown
(Neverdahl et al., 2017)	Reduced SICI in interictal MIG	CO: 33 MIG: 27	Figure-of-eight	APB	2, 4, 6, 8, 10, 15	CS 80 % RMT TS 120 % RMT	TMS and analyses	Similar time of day (blinded)
(Siniatchkin et al., 2007)[3]	Increased ICF in interictal MwoA	CO: 15 (female) MwoA: 16 (female)	Figure-of-eight	ADM	20, 60, 120	CS 110 % RMT TS 110 % RMT	No	Most recordings in the late morning
(Valente et al., 2021)	Lack of SICI in CM	EM: 11 CM: 11	Figure-of-eight	FDI	1, 2, 3, 6, 10, 15	CS 80 % RMT TS 120 % RMT	No	Unknown
(Werhahn et al., 2000)	No interictal difference between groups	CO: 17 MA: 12 FHM: 9	Figure-of-eight	FDI	2, 3, 4, 7, 10, 12, 15	CS 75 % RMT TS 1-2 mV MEP	No	Unknown

CO = Controls; MwoA = Migraine without aura; MA = Migraine with aura; MIG = Migraine; EM = Episodic migraine; CM = Chronic migraine; FHM = Familial hemiplegic migraine; FDI = First dorsal interosseus muscle; ADM = Abductor digiti minimi muscle; APB = Abductor pollicis brevis muscle; RMT = Resting motor threshold; CS = Conditioning stimulus; TS = Test stimulus; SICI = Short interval intracortical inhibition; ICF = Intracortical facilitation

[1]Effects following rTMS is not reported in this table.

[2]Effects following light deprivation and environmental light exposure is not reported in this table.

[3]The authors used unconventional suprathreshold stimulus intensity for ICF CS.

Table 3 Previous studies of short latency afferent inhibition (SAI) in migraine patients

Study	Results	Subjects (n)	Coil type	Target nerve and muscle	ISI (ms)	Stimulation intensity	Blinding	Time of examination
(Alaydin et al., 2019)	No interictal difference between groups Reduced preictal and ictal SAI	CO:16 MwoA: 25[1]	Figure-of-eight	MN, APB	21	CS 200% ST TS 1 mV MEP	TMS and analyses	Assumed similar time of day (blinded)
(Coppola et al., 2020)	Reduced SAI in interictal MwoA Increased SAI in ictal MwoA	CO: 16 MwoA: 30[2]	Figure-of-eight	MN, FDI	N20 + 2, 4, 6, 8	CS 120 % MT TS 120 % RMT	Analyses	Between 2 P.M. and 7 P.M.

ISI = Interstimulus interval; CO = Controls; MwoA = Migraine without aura; MN = Median nerve; FDI = First dorsal interosseus muscle; APB = Abductor pollicis brevis muscle; ST = Sensory threshold; MT = Motor threshold; RMT = Resting motor threshold; CS = Conditioning stimulus; TS = Test stimulus

[1]10 interictal, 5 preictal, 10 ictal.

[2]16 interictal, 14 ictal.

1.7 Event related beta oscillations

Events can lead to time-locked decrease or increase of power in the EEG termed as event related desynchronisation and synchronisation (ERD and ERS). These responses differ from evoked potentials in being non-phase-locked. ERD and ERS is the result of decreases and increases in synchrony of oscillations in the investigated frequency range in the underlying neural population (Pfurtscheller and Andrew, 1999). This method for quantification of EEG-responses was described by Pfurtscheller et al. in the 1970s (Pfurtscheller and Aranibar, 1977). The technique can be applied to investigate interactions between thalamocortical systems and cortical interneurons (Pfurtscheller and Lopes da Silva, 1999, Mykland et al., 2019).

Event related oscillations in the beta frequency band over the sensorimotor area appear to be mostly dependent on afferent stimulation and somatosensory processing during movement and sensory tasks (Nakayashiki et al., 2014, Houdayer et al., 2006, van Wijk et al., 2012, Cassim et al., 2001). It is known from studies in rats that somatosensory input in general evoke feedforward inhibition in the motor cortex from thalamocortical input (Murray and Keller, 2011). Beta-ERD likely also represent increased firing rates of pyramidal tract neurons (van Wijk et al., 2012). Beta-ERD during motor imagery has been associated with reduced SICI (Takemi et al., 2013). For beta-ERS, a linear relation with primary motor cortex GABA concentration has been observed (Gaetz et al., 2011). These observations indicate that beta-ERD during motor imagery and beta-ERS after movement execution are associated with GABAergic inhibition (Gaetz et al., 2011, Takemi et al., 2013). However, another study using MEG reported increased beta-ERD and reduced beta-ERS after administration of tiagabine prior to a movement task. Tiagabine blocks GABA Transporter 1 and increase endogenous GABA activity (Muthukumaraswamy et al., 2013). Because movement related beta-ERS was not affected by the GABA-A modulator diazepam (Hall et al., 2011), the authors interpreted beta-ERS to be GABA-B dependent (Muthukumaraswamy et al., 2013). Thus, opposite effects on beta-ERS were described related to endogenous GABA concentration and medication induced GABA level increase. One review suggested that GABA transport blockade also made a spatially confined signal into an unrestricted wave of inhibition (Scimemi, 2014), possibly explaining differences between endogenous GABA levels and inhibitory changes due to GABA transporter blockade.

Beta-ERD and beta-ERS during movement is often termed as movement related beta decrease (MRBD) and post-movement beta rebound (PMBR) respectively (Barone and

Rossiter, 2021). However, as the beta band responses may not only arise from movement (Houdayer et al., 2006, Miller et al., 2010), using the general terms beta-ERD and beta-ERS together with a specific task type description may be more informative.

Few studies have investigated ERD and ERS in migraine subjects. One study of alpha-ERS during passive auditory stimulation found defect alpha-ERS fading in migraine patients (Yum et al., 2014). Mykland et al. investigated beta-ERD and beta-ERS related to a sensorimotor task like the one applied in this thesis. These studies revealed no difference between interictal migraine patients and healthy controls. However, they observed an increased beta-ERD and beta-ERS in the preictal phase and reduced beta-ERS in the ictal phase compared to the interictal phase (Mykland et al., 2019, Mykland et al., 2018).

2. Aims and objectives

We aimed to demonstrate mechanisms that connect migraine pathophysiology and sleep physiology. The purpose of detecting these mechanisms was to improve our understanding of migraine pathophysiology and the clinically observed migraine-sleep relationship. We also aimed to identify differences in pathophysiology between migraine subgroups. Identifying migraine subgroups with different pathophysiology is necessary to correctly evaluate study results and to develop biomarkers for migraine.

We hypothesised that migraine patients have an underlying dysfunction of brain systems which regulate sleep and wake and that this dysfunction influence thalamocortical systems and regulation of cortical excitability. We hypothesised that because of this dysfunction, insufficient sleep would cause abnormal changes in cortical inhibitory and/or facilitatory effects during the interictal phase and that the effects would change near the migraine attack. We also hypothesised that the sleep-wake related dysfunction may be different between migraine subgroups with attacks predominantly occurring during sleep and attacks usually occurring during the awake state.

We examined TMS-measures which have previously revealed intriguing, but inconsistent results in migraine. These responses represent GABAergic and dopaminergic systems with implied roles in migraine pathophysiology and a relation to circadian systems and sleep-wake regulation. One objective was to examine whether changes in SICI and ICF may indicate a GABA-A and glutamatergic imbalance after insufficient sleep in migraine. Another objective was to examine different aspects of GABA-B mediated inhibition related to circadian rhythm via CSP and LICI. Furthermore, another objective was to examine GABAergic inhibition related to cholinergic systems via SAI. Finally, another objective was to examine beta-ERD, beta-ERS and SAI as measurements of sensorimotor processing.

3. Materials and methods

This thesis is based on data collected between January and December of 2020. The study was paused between 12th of march and 2nd of June due to the Covid-19 pandemic. Data for all three papers were collected from the same subjects on the same examination days. Data was collected at the Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU) in Trondheim, Norway. The methods are described in further detail in the respective papers.

3.1 Subjects

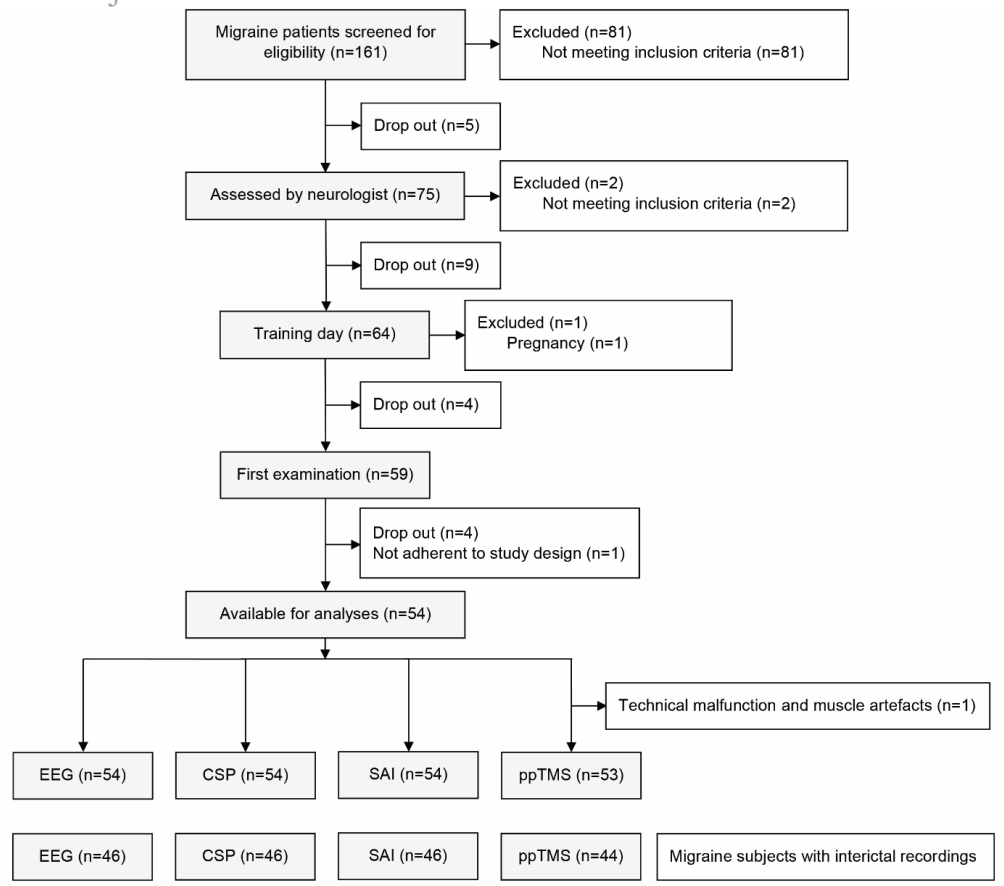

Figure 3 Inclusion flow chart for migraine subjects

Number of subjects at each stage is described in grey boxes and number of subjects eliminated at each stage is described in white boxes.

Subjects between 18 and 65 years of age were recruited for one group of episodic migraine subjects and one age and gender matched group of healthy controls. Migraine subjects were

evaluated according to The International Classification of Headache Disorders, 3rd edition (IHS, 2018) and were required to have on average between 1 and 6 self-reported monthly attacks during the previous six months. Migraine subjects were not allowed to use prophylactic treatment for at least four weeks before the first examination and throughout the study period. Detailed inclusion and number of participants are described in figure 3 and 4.

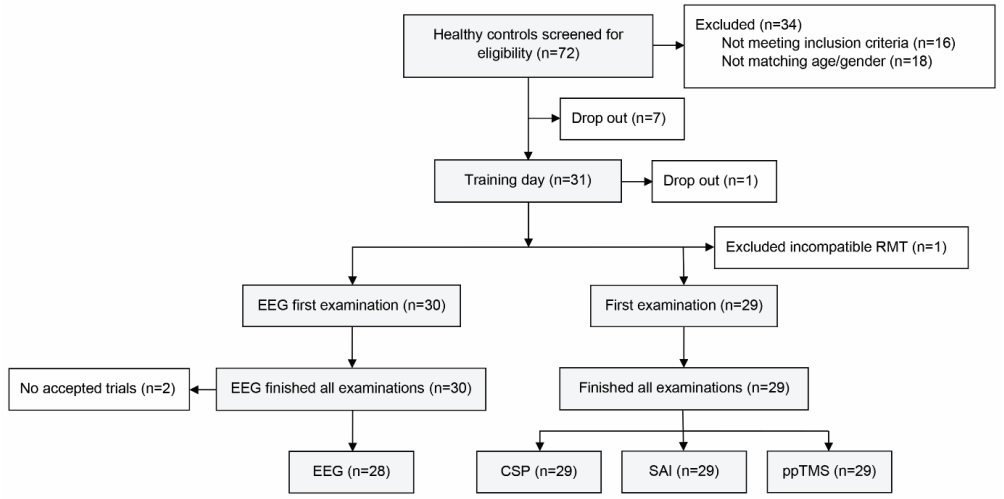

Figure 4 Inclusion flow chart for control subjects

Number of subjects at each stage is described in grey boxes and number of subjects eliminated at each stage is described in white boxes.

3.2 Study design

All subjects attended the laboratory on three different days (Figure 5). The first day was utilised as a training day where all examinations were performed for the subjects to get familiar with the environment, tasks, and equipment. The following first and second examination day was scheduled at the same time for each subject, either at 08:00 or 10:30. Migraine subjects and controls were separately randomised to have the first examination day preceded either by two nights of 8-hour habitual sleep or two nights of 4-hour restricted sleep. The time of examination and order of sleep conditions was similarly distributed between the migraine group and the healthy control group.

Every laboratory session started with a short questionnaire before 10 minutes of psychomotor vigilance test was performed. Then a short session of quantitative sensory testing of pressure-, heat- and cold pain thresholds were conducted. These data are not reported in this thesis.

Afterwards the EEG-based task was performed, before TMS was conducted at the end of the session. A questionnaire was also filled out before the subjects left the laboratory.

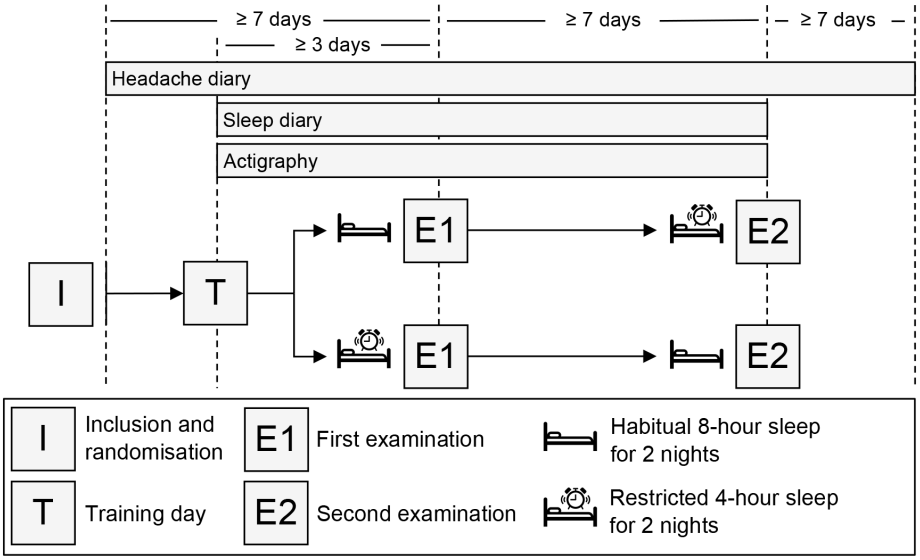

Figure 5 Study design

Illustration of the study design indicating how every participant underwent inclusion and randomisation (I) before attending a training day (T) to get accommodated to the location, setting and equipment. Bars indicate the time period the participants registered a headache diary, a sleep diary and wore an actigraph. Symbols indicate the sleep condition preceding the first and second examination (E1 and E2) in the randomised crossover design.

Subjects filled in a headache diary from at least seven days before the first examination day until at least seven days after the last examination day. They also filled in a sleep diary from the training day until the last examination day. An actigraph (Actiwatch Spectrum Plus, Philips Norge AS, Oslo, Norway) was worn between the training day and the second examination day.

The investigator was blinded for diagnosis and sleep condition. Subjects received repeated instruction to not reveal this information to the investigator prior to examinations.

3.3 Transcranial magnetic stimulation

3.3.1 Equipment and setup

TMS was performed according to the current guidelines (Rossini et al., 2015). Stimulations were delivered through a figure-of-eight MCF-B65 Butterfly Coil. To reliably stimulate the

same location throughout each session, we utilised Localite TMS Navigator without MRI. Every coil stimulation was a biphasic 280 µs pulse initially inducing anteroposterior current in the tissue. We recorded EMG responses from the APB.

3.3.2 Cortical mapping and threshold determination

We located the stimulation location and coil rotation over the left scalp which evoked the largest consistent MEP in APB. We estimated the RMT according to the modified relative frequency criterion which is based on recommendations by Rossini et al. (Rossini et al., 1994) and modified by Groppa et al. in the IFCN guidelines of 2012 (Groppa et al., 2012).

3.3.3 Cortical silent period (CSP)

The participants were instructed to perform isometric abduction of the thumb against a Velcro band at 50 % of maximum voluntary contraction (MVC) force. We recorded 6 trials of CSP with TMS stimulation intensity of 120 % RMT. We adapted the mean consecutive difference (MCD) threshold method by Garvey et al. for automatically detecting the onset and offset of CSP (Garvey et al., 2001, Hupfeld et al., 2020). MEP onset was used as CSP onset. Every CSP was visually inspected for artefacts and breakthrough EMG by a blinded investigator. Breakthrough EMG was included in the CSP (Hupfeld et al., 2020).

3.3.4 Paired pulse transcranial magnetic stimulation (ppTMS)

We recorded the ppTMS subtypes SICI, ICF and LICI. We combined all stimulation types in a continuous session where stimulation order was organised by block-randomisation and each stimulation type separated by randomised 4-, 5- or 6-seconds inter-train interval (ITI). We recorded 20 blocks where every block consisted of the following 6 stimulation types in randomised order: Single TS of 120 % RMT, SICI at 2 and 4 ms ISI with 80 % RMT CS and 120 % RMT TS, ICF at 8 and 10 ms ISI with 80 % RMT CS and 120 % RMT TS and LICI at 100 ms ISI with 109 % RMT CS and 120 % RMT TS.

3.3.5 Short latency afferent inhibition (SAI)

During SAI recording, a stimulator was placed over the median nerve at the wrist with the cathode proximal. The motor threshold was used as stimulation intensity for median nerve CS. SAI was then performed with a fixed ISI of 21 ms (Tokimura et al., 2000) and a TMS TS stimulation intensity of 120 % RMT. We recorded 20 single TS of 120 % RMT and 20 SAI in alternating order with a 5 second interval between.

3.3.6 Data analyses of ppTMS and SAI

Every ppTMS and SAI recording were visually inspected by a blinded investigator and trials with artefacts or baseline EMG activity were excluded. The peak-to-peak amplitude of every

included MEP was measured, and the averaged amplitudes were then transformed to normalise the distribution and limit the "floor effect" (Tankisi et al., 2021). The most appropriate transformation which was to the power of 0.2 was found by box cox transformation.

3.4 Electroencephalography

3.4.1 Equipment and recording

We recorded scalp EEG with electrodes placed according to the international 10-20 system (Chatrian et al., 1985). Electrodes were referenced to a common reference at FCz during recording. We also recorded electrooculography (EOG) of eye movement and EMG of wrist movement.

3.4.2 Sensorimotor task

We used a task for inducing sensorimotor responses which have previously been applied by our research group in another study of migraine subjects (Mykland et al., 2019, Mykland et al., 2018). The first part of the task was for the participant to flex their wrist and hold a flexed position for about 2 seconds, letting their fingertips touch balls of different materials in a spinning bowl. Immediately following flexion, the participants fully extended their wrist for another 2 seconds before letting their arm completely rest. The task was repeated to record a total of 40 trials.

Prior to the test, we informed the participants to make notice of whether their hand touched a metal ball at any time during the 40 trials. We asked the participants whether they noticed metal after each examination day to maintain the perception that this part of the task was important. There was never any metal ball in the bowl. This part of the procedure was applied to maintain attention to the task.

3.4.3 Data analyses of event related beta oscillations

We applied a 1-100 Hz 2nd order IIR Butterworth filter and a 50 Hz notch filter to the EEG data. We then used cubic spline interpolation to acquire a new resolution of 512 Hz. Every trial was visually inspected and trials with artefacts were excluded. Markers were manually placed on start (T1) and end of movement (T2) based on EMG recordings. Ocular artefacts were rejected from EEG by visual inspection of components acquired by fast independent component analysis (ICA). Then, all EEG channels were re-referenced to an average reference. We exported data from the C3 electrode filtered to 13-24 Hz using a 2nd order IIR Butterworth filter for analyses. We used custom made scripts in MATLAB to calculate beta-

ERD/ERS from 13-24 Hz filtered data. The method used was the intertrial variance protocol described by Kalcher and Pfrutscheller (Kalcher and Pfurtscheller, 1995).

3.5 Statistical analyses

Statistical analyses are described in detail in the respective papers. Every statistical analysis was carried out in STATA. We applied linear mixed models for every analysis. These models are suited to handle missing data and repeated measures and are consequently appropriate for our study design where migraine subjects may have their examination days in different migraine phases. Linear mixed models make assumptions of linearity, independence, homoskedasticity and normality on residuals and random effects at different levels. Assumptions were investigated by inspection of histogram plots and q-q plots. Box cox regression was applied when transformation of the outcome variable was necessary. The model most appropriate was determined as the model giving the lowest Akaike and Bayesian information criterion (AIC/BIC) among theoretically appropriate random intercept and random slope models with different covariance structures and number of levels. Two-sided p-values < 0.05 were reported as significant. We did not adjust for multiple comparisons as such procedures assume all null hypotheses to be true simultaneously (Perneger, 1998).

4. Synopsis of results

The main results of this study are summarised in table 4 and 5 in the general discussion.

4.1 Interictal migraine patients compared to controls

Sleep restriction had different effects on CSP duration in migraine patients and controls where the CSP inhibitory effect became shortened in migraine patients (Paper I). A similar effect was seen when replacing sleep condition with measured total sleep time in the model. The effect persisted with the covariate days since start of last menstruation added to the initial model.

We observed associations between CSP and several clinical variables. Sleep restriction decreased CSP duration more in migraine patients with frequent attacks, greater degree of photophobia, phonophobia and osmophobia, and premonitory yawning. For combined sleep conditions, shorter CSP was seen with higher allodynia score during attacks, greater degree of photophobia, phonophobia and osmophobia, premonitory yawning and premonitory mood changes.

4.1.1 Interictal sleep related migraine

LICI was decreased after sleep restriction in sleep related migraine compared to controls (Paper I).

Beta-ERS % was decreased after sleep restriction in sleep related migraine compared to controls and non-sleep related migraine (Paper III). The effect of sleep restriction on beta-ERS % within the sleep related migraine group was also significant.

4.1.2 Interictal non-sleep related migraine

CSP duration were shorter after sleep restriction in non-sleep related migraine compared to controls and sleep related migraine (Paper I). The effect of sleep restriction on CSP duration within the non-sleep related migraine group was also significant.

4.1.3 Interictal migraine patients with aura

Shortened CSP duration after sleep restriction was also seen for the migraine with aura subgroup compared to controls (Paper I).

4.1.4 Interictal migraine patients without aura

SICI at 4 ms was increased after sleep restriction in migraine patients without aura compared to controls (Paper I).

SAI was reduced after sleep restriction in migraine patients without aura compared to controls and migraine patients with aura (Paper I).

4.2 The period leading up to a migraine attack

LICI increased and SAI decreased more after sleep restriction the shorter time that remained to the coming migraine attack. We observed an association between the larger LICI increase and higher usual migraine headache intensity. In secondary analyses, LICI also increased after sleep restriction in the preictal compared to the interictal phase. LICI was reduced after habitual sleep preictally (Paper II).

4.3 The period following a migraine attack

SICI at 2 ms was more reduced after sleep restriction with shorter time elapsed since the end of the previous attack, and for the postictal phase compared to the interictal phase in secondary analyses. We also found increased ICF 8 ms and ICF 10 ms after sleep restriction in the postictal compared to the interictal phase (Paper II).

Beta-ERD % was more increased and beta-ERS % more reduced after sleep restriction with shorter time elapsed since the end of the previous attack (Paper III).

5 Methodology discussion

5.1 Transcranial Magnetic Stimulation

5.1.1 Waveforms and current direction

Traditionally monophasic posteroanterior (PA) current has been most frequently used for ppTMS due to historical reasons and initial technical availability (Davila-Perez et al., 2018). We instead chose biphasic pulses initially inducing anteroposterior (AP) current in the tissue, i.e. a AP-PA stimulation. Similar settings have been applied by our research group in a previous study of TMS in migraine patients (Neverdahl et al., 2017). Another study of ppTMS in migraine also applied biphasic stimulation (Conforto et al., 2012), but type of stimulation and current direction is often not reported in previous studies in migraine subjects (Cosentino et al., 2018, Valente et al., 2021, Werhahn et al., 2000, Brighina et al., 2010, Brighina et al., 2005). We based the decision of AP-PA stimulation on the different properties pertaining to the various TMS-responses and current types.

PA and AP monophasic and biphasic stimulation evokes different indirect waves (I-waves) of corticospinal activity suggested to originate from indirect, transsynaptic activation of cortical pyramidal tract neurons (Di Lazzaro et al., 2012). PA current direction mainly evoke early I1-waves while AP current direction mainly evoke later I-waves (Wessel et al., 2019), possibly produced from horizontal cortico-cortical connections which originate from other regions such as the thalamus (Davila-Perez et al., 2018). The SICI effect at 3 ms ISI has been observed to differ between PA and AP based stimulation, where AP current direction produced stronger inhibition (Wessel et al., 2019, Hanajima et al., 2008, Di Lazzaro et al., 2008). The SICI effect may mostly depend on the later I-waves and consequently AP current direction may be of interest when measuring SICI (Wessel et al., 2019, Nakamura et al., 1997, Di Lazzaro and Ziemann, 2013). However, some authors have in contrast produced stronger SICI with monophasic PA (Davila-Perez et al., 2018). For threshold tracking TMS, AP was shown to be superior to PA for SICI measurements (Cirillo and Byblow, 2016).

Biphasic stimulation can be viewed as two opposite monophasic pulses (Sommer et al., 2018) producing I-waves with different latency and wave distribution (Di Lazzaro et al., 2008), and is possibly less dependent on direction (Davila-Perez et al., 2018). The AP-PA stimulation is most efficient for stimulating the cortico-spinal pathway (Davila-Perez et al., 2018). At increasing stimulation intensities, the AP-PA pulse also produce a pattern of waves that resembles that of the traditional monophasic PA (Di Lazzaro et al., 2008), including gradually larger late I-waves (Davila-Perez et al., 2018). In addition, both ICF and SCI has

been shown to be comparable between AP-PA stimulation with the equipment used in this study (MagVenture MagPro X100) and the traditional Magstim PA (Wessel et al., 2019).

Other authors have shown that AP-PA produce more reliable ICF, where monophasic PA pulses lacking the AP component, did not produce significant ICF (Davila-Perez et al., 2018). This may be expected as ICF do not produce changes in I-waves, suggesting longer range connections to be involved. These connections may be from premotor cortex, similarly to those which appear to only be activated by AP (Di Lazzaro and Ziemann, 2013). The authors also found that monophasic AP produced more reliable LICI than PA (Davila-Perez et al., 2018). As with SICI, LICI is thought to represent suppression of late I-waves (Di Lazzaro and Ziemann, 2013), possibly explaining this finding. AP-PA has also been shown to produce longer CSP than monophasic stimulation (Davila-Perez et al., 2018). In summary, the cellular effects differing between waveforms and current direction need further investigating. Based on the current knowledge, the biphasic waveform with AP-PA current direction was considered appropriate for investigation of SICI, ICF, LICI, CSP and SAI in the present study.

5.1.2 Left hemisphere abductor pollicis brevis representation

The motor cortical representation of hand muscles is located in the precentral gyrus close to the middle genu of the central sulcus and is known as the hand knob (Boroojerdi et al., 2000). Due to the availability of this location on the brain surface, this area has been used as a target for TMS since the beginning in 1985 (Barker et al., 1985, Boroojerdi et al., 2000). The area offers opportunity for stimulation of several target muscles such as the APB and the first dorsal interosseus muscle (FDI) (Boroojerdi et al., 2000, Wassermann et al., 1992). In the present study, the cortical area of the left hemisphere corresponding to APB was stimulated in all participants. The reliability of cortical mapping of APB have been shown in several studies with reproducible maps between sessions for the same subjects and for different electrode spacing configurations (Thickbroom et al., 1999, Mortifee et al., 1994, Corneal et al., 2005).

While there are descriptions of dominant/non-dominant hemisphere differences in CSP (Priori et al., 1999), most reports of CSP have not produced significant hemispheric differences (Cicinelli et al., 1997, Saisanen et al., 2008, Menon et al., 2018). Investigations of SICI and ICF did also not reveal significant differences between the dominant and non-dominant hemisphere (Menon et al., 2018). Consequently, we chose to stimulate the left hemisphere in all subjects as left-right differences in migraine pathophysiology may be

theoretically possible based on previous studies (Schulte et al., 2020b, Mykland et al., 2019, Mykland et al., 2018). We did not subgroup migraine subjects by headache side of the most recent/next attack due to sample size of the migraine phases subgroups. Thus, applying TMS to the left hemisphere only may theoretically reduce group differences. Applying bilateral TMS could avoid this issue but would introduce challenges in analyses regarding how to weight the different sides in each subject. Whether usually headache side or left and right hemisphere separately should be compared in such analyses is currently unknown.

5.1.3 Motor threshold determination

We applied the modified relative frequency criterion when measuring RMT. This approach requires time and occasionally a large number of stimuli. Consequently, adaptive methods have been developed in an attempt to reduce the time and number of stimuli required to obtain a motor threshold (Groppa et al., 2012). In our study design, we utilised the training day to standardise the procedure to each participant and consequently achieved a reduction in time spent for motor threshold determination and a more similar number of stimuli required between participants. However, methods based on parameter estimation by sequential testing (PEST) and maximum likelihood regression is validated and may be suggested in future studies (Groppa et al., 2012, Mishory et al., 2004, Awiszus, 2003, Awiszus, 2012, Rossini et al., 2015).

5.1.4 Cortical silent period (CSP)

Many studies evaluating CSP use different methods or do not report the complete methodology. To combat this issue, Hupfeld et al. published a review and suggestions for increased consistency in CSP studies in 2020 (Hupfeld et al., 2020). First, the coil type may be of greater importance for CSP than for other single and paired pulse TMS paradigms (Badawy et al., 2011). Using a figure-of-eight coil, as in the present study, may produce shorter CSP duration than a circular coil (Badawy et al., 2011, Hupfeld et al., 2020).

The procedures for CSP presented by the IFCN suggest a protocol with 5-6 trials per muscle (Groppa et al., 2012, Rossini et al., 2015). However, while no difference in CSP have been found when increasing number of trials from 10 to 50 (Garvey et al., 2001), it is suggested that a greater number of trials may make a more precise estimation (Groppa et al., 2012, Hupfeld et al., 2020). We adhered to the IFCN suggestions of 6 trials for CSP in this study, although there is a chance that a protocol with a larger number of trials may yield greater precision (e.g. 10-30 trials).

There is great variation in protocols for applied level of muscle force in various CSP studies. Results are generally inconsistent as to whether the applied force affect the CSP duration (Hupfeld et al., 2020). We utilised a force goal of 50 % of MVC. This force level has been shown to be appropriate for recording CSP in APB, where 40-60 % MVC was easy to obtain and maintain. In fact, muscle contraction force between 20 % and 80 % did not have any effect on CSP in APB, indicating low level of control needed (Saisanen et al., 2008). Thus, we evaluated and controlled the contraction force in cooperation with the participant and by visual evaluation of EMG during contraction.

EMG was monitored throughout the procedure to avoid fatigue (Hupfeld et al., 2020). We used a 12 second interval between each contraction which is longer than what was applied by Säisänen et al. (6-10 seconds) (Saisanen et al., 2008) and should allow for appropriate resting time between trials. We also applied an isometric task as is recommended by some authors (Mathis et al., 1999).

We applied 120 % RMT, because Säisänen et al. showed that this stimulation intensity induced CSP in all participants, produced the lowest CSP duration variation and yielded similar CSP duration between the hemispheres (Saisanen et al., 2008). 120 % RMT should therefore be an optimal intensity for obtaining stable and informative CSP in APB.

One challenge in determining the duration of CSP is the varying induction of breakthrough EMG activity during the CSP. This activity is considered to be of spinal origin (Zeugin and Ionta, 2021), and should not be counted as the end of the CSP (Hupfeld et al., 2020). However, current recommendations suggest that authors report the ratio of trials and subjects with breakthrough EMG to inform future studies of expected findings (Hupfeld et al., 2020). We reported the percentage of participants with breakthrough EMG in paper I, which was similar between groups, but slightly higher in migraine subjects (25.5 %) than controls (17.2 %).

Another challenge in the CSP duration determination is how to identify CSP onset and offset. The onset has most commonly been defined at the TMS pulse or as either the start or end of the MEP preceding the CSP. The offset has in some studies been set by visual inspection which leave large room for variation when the EMG activity returns gradually. Consequently, implementing an automatic method has been suggested and the MCD threshold method by Garvey et al. is recommended (Hupfeld et al., 2020, Garvey et al., 2001). We applied an adapted version of the MCD threshold method (Garvey et al., 2001) where we defined the

start of MEP instead of the end as the CSP onset to minimise possible error due to gradual EMG decay at the end of the MEP (Saisanen et al., 2008). The protocol is described in detail in paper 1, and we suggest applying this method in future studies of CSP.

5.1.5 Paired pulse transcranial magnetic stimulation (ppTMS)

The suggested number of trials by the current IFCN guidelines is at least 8-10 measurements of each ppTMS stimulation type (Rossini et al., 2015). However, other authors suggest that 20-30 trials are necessary to maintain good within- and between-session reliability, with no additional benefit above 30 trials (Goldsworthy et al., 2016, Biabani et al., 2018, Brownstein et al., 2018, Chang et al., 2016). Simultaneously, they recognise that prolonged recording sessions may not be practically feasible (Goldsworthy et al., 2016). We accordingly chose to record 20 trials of each stimulation type.

The SICI type inhibition appears to consist of two different phases which peaks at ISIs around 1 ms and 2.5 ms (Rossini et al., 2015, Fisher et al., 2002). We chose to investigate ISIs of 2 and 4 ms which mainly covers the second of these phases. SICI around 2.5 ms ISI range represent the post-synaptic GABA-A related inhibitory mechanisms which is often described as the SICI-effect. The phase around 1 ms may instead represent refractory corticospinal neurons combined with synaptic inhibition or extrasynaptic GABA tone (Rossini et al., 2015, Fisher et al., 2002, Hanajima et al., 2003, Roshan et al., 2003, Stagg et al., 2011). Further increasing ISIs of SICI also likely represent decreased inhibitory effect in a measure of inhibitory/facilitatory balance (Rossini et al., 2015).

In addition to the conventional MEP amplitude-based method of assessing ppTMS which we applied in this study, ppTMS may also be measured by threshold tracking methods (Nielsen et al., 2021, Vucic et al., 2006, Fisher et al., 2002). These methods use a predefined target MEP amplitude and track the change in stimulus intensity needed to evoke the target MEP. Thus, the relative change in intensity is the outcome variable of this technique (Nielsen et al., 2021). The method was initially thought to avoid the limiting “floor effect” of the conventional method. This effect occurs when inhibition approaches 100 % and small or no MEPs are recorded. It was also suggested that threshold tracking limit spinal and peripheral contributions to the measurement (Tankisi et al., 2021, Fisher et al., 2002). Tankisi et al. found that one also may avoid the “floor effect” by using the geometric mean of MEP amplitudes and logarithmic transformation to normalise MEP data (Tankisi et al., 2021). This technique resembles the method of transforming to the power of 0.2 as applied in this study. This transformation normalises the distribution of MEP amplitudes including those close to 0

but does not solve the problem of the "floor effect" occurring at complete inhibition. Furthermore, Tankisi et al. also showed that the threshold tracking method for evaluating SICI at different ISIs in series has severe limitations pertaining to how one initialises tracking and suggested that thresholds should be estimated independently for each ISI. A method tracking randomised ISIs in parallel instead correlated well with the conventional amplitude-based SICI. They also suggested that the conventional method may be more sensitive to loss of inhibition and that threshold tracking does not improve MEP variability. On the other hand, threshold tracking displayed adequate-to-excellent intra- and inter-day reproducibility while conventional SICI had poor intra- and poor-to-adequate inter-day reproducibility (Tankisi et al., 2021). Vucic et al. has also argued that threshold tracking is feasible and reproducible for SICI, ICF and LICI (Vucic et al., 2006). For SAI examination, the normalisation of conventional amplitude-based SAI resulted in smaller within-subject variability than threshold tracking (Cengiz et al., 2022). In conclusion, the conventional amplitude-based method of recording ppTMS and SAI appear to be a good choice for detecting potential loss of inhibition. A parallel type tracking method may be considered in the future to avoid the "floor effect" of complete inhibition which is often seen censoring larger inhibition effects for LICI and SAI, and which we also observed in the present study.

Siniatchkin et al. have applied a suprathreshold CS of 110 % RMT for ICF measurements in migraine patients. This method did not induce any facilitation in healthy controls, but instead a large facilitation in migraine patients (Siniatchkin et al., 2007). However, the conventional recommended method for ICF is to utilise subthreshold CS (Rossini et al., 2015) which we consequently applied in this study. The mechanisms of the suprathreshold CS ICF used by Siniatchkin et al. is unknown.

5.1.6 Short latency afferent inhibition (SAI)

SAI can be recorded with a predefined interval between the TMS pulse and the peripheral nerve stimulation or the interval can be set relative to the N20 latency of the individual participants. During the planning of the present study, it was uncertain whether the individual adjustments provided any added precision to the measurement (Turco et al., 2018). As the only study of SAI in migraine subjects available at the time of the present study was conducted with predefined ISI of 21 ms (Alaydin et al., 2019), we also applied a similar method with predefined ISI. Since then, another study using individual ISI in migraine participants has been published (Coppola et al., 2020). However, more recent results have demonstrated that the measurement error is similar between the methods indicating similar

reliability. Turco et al. have consequently suggested that the individual approach is unnecessary (Turco et al., 2019, Turco et al., 2021). Thus, we conclude that our approach with a predefined ISI was appropriate for this study.

The inhibitory SAI effect is greater for larger nerve stimulation intensity (Turco et al., 2018). Bailey et al. found that the inhibitory effect increases until it is saturated at about 1.2 times the motor threshold. This saturation occurred at about 50 % of the maximum sensory nerve action potential for median nerve stimulation (Bailey et al., 2016). SAI has also been shown to decrease immediately after acute pain (Burns et al., 2016) and increasing median nerve stimulation may be painful. Bailey et al. suggested that this effect may have contributed to a decrease in SAI at higher median nerve stimulation intensity of about 71 % of maximum sensory nerve action potential (Bailey et al., 2016). We chose the motor threshold as CS for SAI recording. However, the effect of nerve stimulation intensity may be less variable with higher stimulation intensities. On the other hand, we do not know how the increased pain from higher intensities would affect measurements in healthy controls and migraine patients (Turco et al., 2018). We found the motor threshold level of stimulation intensity to be a feasible middle ground choice.

5.1.7 Motor threshold drift

SAI were recorded at the end of the TMS session, and the MEP amplitude from TS recorded during SAI appear to be lower than in the preceding 10 min of ppTMS (habitual sleep ppTMS TS 1.07 mV 0.56-2.26 IQR; habitual sleep SAI TS 0.89 mV 0.50-1.26 IQR; sleep restriction ppTMS TS 1.52 mV 0.93-2.85 IQR; sleep restriction SAI TS 1.09 mV 0.73-1.70 IQR). It is known that the RMT may change throughout the recording both due to biological and technical factors (Samusyte et al., 2018). Possible effects of moving away from the "hotspot" were avoided in this study with navigation during TMS. However, such effects may also be due to a motor threshold drift, which is accounted for in threshold tracking methods (Samusyte et al., 2018). These methods may therefore be preferable in recordings of the length used in this study. However, to account for MEP variance throughout the session we distributed TS between recordings of conditioned measurements during both ppTMS and SAI.

Low frequency rTMS, often using 1 Hz stimulation frequency, is known to have effects on cortical excitability. Additionally, lasting effects on excitability has also been investigated for 0.1 Hz rTMS of 10-minute duration (Rossini et al., 2015). Thus, this stimulation frequency encompasses the inter-train interval ITI we used for ppTMS of randomised 4, 5 or 6 seconds.

However, while low frequency rTMS of 0.9 Hz may depress cortical excitability for 15 minutes, 0.1 Hz may not be able to induce these effects (Chen et al., 1997, Fitzgerald et al., 2006). Another study found some effects of subthreshold 0.2 Hz rTMS over premotor cortex, improving hand writing and prolonging CSP (Murase et al., 2005). Most notably, Thickbroom et a. investigated 0.2 Hz rTMS with paired pulses of 1.5 ms ISI following I-wave periodicity. This protocol increased the MEP amplitude after stimulation, but did not affect the motor threshold (Thickbroom et al., 1999). In a similar study, Sommer et al. performed rTMS with SICI and ICF at 0.17 to 5 Hz frequency. Only frequencies from 1 Hz and higher induced lasting effects in this study (Sommer et al., 2001). In contrast, Ikeguchi et al. found reduced excitability after 0.2 Hz subthreshold rTMS of 180 single pulses (Ikeguchi et al., 2005). Of note, MEPs after single pulses recorded at 5 s intervals appear to depend on prior corticospinal activation from the previous stimulation (Möller et al., 2009). Previous IFCN guidelines have suggested at least 3 second ITI between single MEP measurements (Rothwell et al., 1999), but recent guidelines provide no clear recommendation for ITI during ppTMS recording (Rossini et al., 2015). Some previous ppTMS based studies have used longer ITIs of 10 seconds (Cosentino et al., 2018) and 7-9 seconds (Werhahn et al., 2000), while other studies have applied 4-6 second ITIs similar to this study (Nieminen et al., 2019) and shorter ITIs such as 3 seconds (Rawji et al., 2021). It is not clear whether our ppTMS protocol of randomised 4, 5 or 6 second ITI induced any lasting effects on cortical excitability, but such effects may be possible.

5.2 Electroencephalography

One important point to consider when examining scalp EEG is the contamination by EMG activity. This is an important and limiting factor for frequencies above 20 Hz. However, the contamination is lowest in the central regions that were analysed in this study. Over central electrodes, the muscle activity contributes to a 1 to 6-fold power increase of frequencies between 25 and 30 Hz. Thus, we chose an upper limit of our beta band of interest at 24 Hz to limit the contamination by muscle activity (Whitham et al., 2007). The lower limit of our beta band was set to 13 as beta band responses to hand activity have been observed down to this cut off (Pfurtscheller et al., 2000, Pfurtscheller et al., 1997). We applied a 2nd order IIR filter to avoid steep slopes and filter artefacts. Thus, also allowing great temporal precision. On the other hand, this filter yields lower precision in the frequency domain (Luck, 2014). However, we chose a beta band with low chance of including frequencies outside of the beta range.

Beta-ERD occur not only during motor execution and imagery, but also during motor planning (Nakayashiki et al., 2014, van Wijk et al., 2012). Consequently, we applied a study design where the task started abruptly after a cue with randomised intervals. This also allowed for a comparative baseline period before the time of the cue.

The sensorimotor task applied in this study was chosen based on previous evaluations of a pure motor task and a combined motor and sensory task in a previous study by our group. The sensorimotor task elicited larger ERD, as expected as beta-ERD and beta-ERS reflect mainly sensory processing (Mykland et al., 2019).

5.3 Definition of migraine phases

We defined the interictal phase as starting 24 hours after resolution of a migraine attack and ending 24 hours before commencement of the next attack, but it is unclear how one should define this interval in studies of migraine pathophysiology. Some migraine patients do not experience premonitory or postdromal symptoms, making a symptomatic characterisation of the interval difficult. Additionally, it is not known whether preictal and postictal mechanisms occur abruptly or gradually over time and how the duration of such mechanisms vary between individuals and between separate attacks. Some authors have suggested the preictal phase to last up to 48 hours before an attack and for the postictal phase to last 24 hours after attacks (Peng and May, 2020). However, in studies looking to advance knowledge of such mechanisms, different approaches should be used in attempts to cover this gap of knowledge. Reliable predictive symptoms occur mainly during the 24 hours closest to attack commencement (Giffin et al., 2003). Investigating changes during this time interval appear reasonable to capture preictal mechanisms. However, such investigations likely encompass an average of early and late preictal and possibly interictal mechanisms if one assumes inter- and intradindividual variation in preictal phase duration. We also examined gradual changes over the interval preceding and following attacks to evaluate possibly gradually changing properties of the phases.

5.4 Caffeine consumption

We did not allow for consumption of caffeine on the day of testing because acute caffeine intake may have effects on CSP or ICF (Turco et al., 2020). However, there is a possibility that participants with high daily caffeine consumption may have been subject to caffeine withdrawal during examinations. It is not known what effects such withdrawal may have on the applied measurements.

5.5 Study design

Low reproducibility has been an issue in several fields of neuroscience (Marek et al., 2022, Button et al., 2013), with migraine research being no exception. Some authors have suggested that conflicting results may be a result of heterogeneity within the migraine diagnosis (Cosentino et al., 2014b). However, several methodological issues such as poor blinding and lack of power have been a consistent limitation in many studies (Sand, 2014, Button et al., 2013) (Table 1-3). Several research fields have shown a risk of overestimation from lack of blinding (Omland et al., 2016). Thus, well powered studies with predefined protocols to reduce biases are needed. Differences between migraine phases should also preferably be investigated with subjects as their own controls (Sand, 2014). Investigations of consecutive repeated measurements during the same migraine cycle may also be beneficial.

The investigator in the present study was blinded for both diagnosis and sleep condition. The same investigator was also blinded during data analyses. Unblinding was not performed until predefined statistical analyses were ready to be executed. This precaution allows for similar instructions to subjects during examinations and consistent recording procedures. Potential biases in how data are evaluated and processed are also avoided (Omland et al., 2016). To both allow blinding and to further avoid biases in time of recording (Lang et al., 2011), every subject had their examinations at the same time in the morning, chosen between two available time slots. Time points, age and gender were matched between migraine subjects and controls. We also added a training day as a first visit to reduce learning effects.

In this study, we applied a longitudinal crossover design. This study design is appropriate for investigating subjects as their own controls after different exposures and lowers selection bias (Redelmeier, 2013). Consequently, this study design is appropriate for investigating differences within the same migraine phase. However, some subjects had examinations in different phases which is a limitation for the phase-comparing analyses.

5.6 Statistical analyses

Combining longitudinal migraine phase analyses with different exposures require appropriate statistical models. We performed statistical analyses with linear mixed models which is an extension to linear regression, allowing clustering of data on different levels and random effects. Such models are advantageous over the traditional repeated measurement analysis of variance (ANOVA) in analyses of repeated measurements. The linear mixed models allow for heterogeneity within and between subjects and for missing data across the levels of the repeated measurements variable (Keselman et al., 2001, O'Connell and McCoach, 2004). In

this way the linear mixed models utilise information on variation to improve the statistical model when different exposures are added to the longitudinal migraine phase design.

In paper II, we analysed examinations from different migraine phases. These analyses introduce apparent limitations such as reduced statistical power in small phasic subgroups. Analyses of these subgroups only had *a posteriori* sample sizes sufficient to evaluate large effect sizes. We applied the Kenward-Roger approximation to improve the performance of the analyses in small samples. However, these secondary analyses should be considered preliminary. This same issue does not apply for the main analyses of gradual changes up until the attack commencement and after attack resolution.

Multiple statistical analyses utilising linear mixed models were carried out in this study. Adjusting for multiple testing in repeated measurements and linear mixed models is challenging (Bender and Lange, 2001). Some also argue that correcting for multiple testing assumes the global null hypothesis to be true and should not be conducted in cases where this is not applicable. Instead, the conduction and interpretation of significance tests should be described in detail. Decreasing the chance of type I errors at the cost of increased risk of type II errors is also not always beneficial (Perneger, 1998, Rothman, 1990, Rothman, 2014). This is also reasonable in studies with an exploratory component where a clear structure in multiple testing is lacking. In these cases one may argue for only considering the comparisonwise error rate (Bender and Lange, 2001). In the present study, the multiple testing structure is unclear and complex, and most significance tests are applied to isolated hypotheses with only a comparisonwise error rate to consider. Thus, we chose to not correct for multiple testing in the present study.

6. General discussion

The main interictal finding in this thesis was reduced CSP duration after sleep restriction in migraine patients compared to healthy controls. The finding was also associated with greater number of attacks per month, increased ictal photophobia, phonophobia and osmophobia, and premonitory yawning. Shorter CSP duration in general was associated with increased ictal hypersensitivity in the form of allodynia, photophobia, phonophobia and osmophobia, and premonitory yawning and mood change. When subgrouping the migraine patients by aura and sleep related attacks, the observed effects of sleep restriction on CSP only occurred in non-sleep related migraine and migraine with aura. For sleep related migraine we observed an interictal decrease in LICI and beta-ERS after sleep restriction. In interictal migraine patients without aura, SICI increased, and SAI decreased after sleep restriction (Table 4).

In the period leading up to a migraine attack, LICI increased, and SAI decreased more after sleep restriction closer to attack commencement. A similar effect on LICI was found for the 24-hour preictal phase specifically (Table 5). After habitual sleep, LICI was reduced preictally.

After attacks, SICI and beta-ERS were more reduced and beta-ERD more increased after sleep restriction close after attack cessation. For the 24-hour postictal phase specifically, a similar effect was seen for SICI, accompanied by increased ICF after sleep restriction (Table 5).

Table 4 Interictal effects of sleep restriction

	Migraine	Sleep related migraine	Non-sleep related migraine	Migraine with aura	Migraine without aura
CSP	↓		↓	↓	
SICI					↑[1]
ICF					
LICI		↓			
SAI					↓
Beta-ERD					
Beta-ERS		↓			

CSP = Cortical silent period; SICI = Short interval intracortical inhibition; ICF = Intracortical facilitation; LICI = Long interval intracortical inhibition; SAI = Short latency afferent stimulation; ERD = Event related desynchronisation; ERS = Event related synchronisation

[1]Increased SICI 4 ms, not SICI 2 ms.

Table 5 Effects of sleep restriction by migraine phase compared to the interictal phase

	Preictal[1]	Postictal[2]
CSP		
SICI		↓[3]
ICF		↑
LICI	↑	
SAI	↓	
Beta-ERD		↑
Beta-ERS		↓

CSP = Cortical silent period; SICI = Short interval intracortical inhibition; ICF = Intracortical facilitation; LICI = Long interval intracortical inhibition; SAI = Short latency afferent stimulation; ERD = Event related desynchronisation; ERS = Event related synchronisation

[1]Including results with a gradual change from 1 week before, until commencement of an attack.

[2]Including results with a gradual change from the attack resolution until 1 week after an attack.

[3]Only for SICI 2 ms.

6.1 Insufficient sleep alters GABAergic and dopaminergic systems interictally

The observed interictally reduced CSP after sleep restriction is likely most dependent on GABA-B receptor mediated inhibition of motor cortical output. However, short CSP duration below 100 ms and long CSP duration above 200 ms is regulated by GABA-A related mechanisms (Ziemann et al., 2015, Hupfeld et al., 2020). The mean CSP duration in this study was about 140-150 ms. Thus, it is likely that the GABA-A related regulation of CSP do not explain the sleep restriction induced changes we observed. CSP and LICI, which are both GABA-B mediated, have been observed to gradually decrease throughout the day. This association may be related to CRH produced in the PVN of hypothalamus (Lang et al., 2011). As described in the introduction, the function of the hypothalamus may be altered in the preictal phase of migraine. However, hypothalamic function may also already be altered in the interictal phase, as studies have shown altered functional connectivity between hypothalamus and several brain regions in the interictal phase. One of these regions were the nucleus caudatus which interestingly has been shown to be associated with arousal and display a lower degree of recruitment during executive tasks in patients with insomnia (Moulton et al., 2014, Stoffers et al., 2014). While we did not observe any interictal changes in LICI in this study, it is possible that the changes in CSP are related to circadian mechanisms of the PVN. Additionally, the effects of sleep restriction on LICI were altered preictally. The circadian variation in CSP or different preceding sleep duration may also be a possible explanation for the variation in previous studies of CSP in migraine, as time of day

during recording is not described in most studies (Table 1). Systematic differences between groups in time of examination during the day would be expected to introduce bias.

Table 6 Current understanding of the mechanisms of the measured effects

Effect	Mechanism
CSP	Duration of GABA-B mediated inhibition from inhibitory post synaptic potentials. Short inhibition < 100 ms is lengthened by presynaptic GABA-A and long inhibition > 200 ms is shortened by presynaptic GABA-A. Lengthened by D1/D2 agonist and levodopa.
SICI	Post synaptic inhibition from α2 and α3 subunits of GABA-A receptors. Controlled by presynaptic GABA-B receptors. Increased by D1/D2 and D2/D3 agonist, decreased by D2 antagonist.
ICF	Net facilitatory effect of excitatory NMDA receptors and inhibitory GABA-A receptors. Decreased by D2/D3 agonist.
LICI	Magnitude of GABA-B mediated slow inhibitory post synaptic potentials. Dependent on GABA in synaptic cleft and presynaptic GABA-B.
SAI	Inhibitory effect of α1 subunits of GABA-A receptors and thalamocortical cholinergic input modulating basket cells. Contribution from recruitment of motor cortex inhibitory interneurons via projections from somatosensory cortex.
Beta-ERD	Increased firing rate of pyramidal tract neurons, reduced by GABA-A mediated inhibition.
Beta-ERS	GABA-B mediated inhibition dependent on GABA concentration.

CSP = Cortical silent period; SICI = Short interval intracortical inhibition; ICF = Intracortical facilitation; LICI = Long interval intracortical inhibition; SAI = Short latency afferent stimulation; ERD = Event related desynchronisation; ERS = Event related synchronisation

Dopaminergic mechanisms increase CSP duration. Accordingly, dopaminergic mechanisms may be of importance for the effects of sleep restriction on CSP in this study. It is not fully known what parts of the dopaminergic systems that regulated CSP, but D1 receptors may be important and dopaminergic inhibition of striatal cholinergic interneurons have been suggested to alter CSP in Parkinson patients. Other mechanisms outside of the striatum may also be involved (Priori et al., 1994, Ziemann et al., 1996, Korchounov et al., 2007). Interestingly, 'dopaminergic' symptoms such as osmophobia, yawning and mood change (Guven et al., 2018) were also associated with shorter CSP in this study. Yawning may be elicited by D2 receptor activation and inhibited by D1 receptor activation. We also note that increased levels of circulating estrogens inhibit yawning and that fall in estrogen during menstrual cycle is associated with the initiation of migraine attacks (Sanna et al., 2012, Argiolas and Melis, 1998, Chai et al., 2014). Premonitory yawning and allodynia are associated in migraine patients (Guven et al., 2018, Barbanti et al., 2020a), and allodynia and yawning had similar associations to CSP in this study. Furthermore, the dopamine metabolite DOPAC have been found to be increased in cerebrospinal fluid during migraine attacks

(Castillo et al., 1996). Altered density of dopamine receptors on lymphocytes in migraine subjects may also indirectly indicate central alteration of dopamine receptors in migraine (Barbanti et al., 1996, Barbanti et al., 2000, Barbanti et al., 2013). In summary, dopaminergic mechanisms appear likely to be related to the inhibitory alterations we observed.

Migraineous headache have been described by people with electrodes implanted in the periaqueductal gray region and activation of ventrolateral periaqueductal gray have been seen during a migraine attack with positron emission tomography (PET) (Bose et al., 2018, Raskin et al., 1987, Weiller et al., 1995). Dopaminergic cells in ventral periaqueductal gray matter have waking effects through projections to thalamus and other wake-sleep regulators (Lu et al., 2006). The ventral periaqueductal gray is also known to be involved in pain regulation (Li et al., 2016) and have previously been implied in migraine pathophysiology. Both D1 and D2 receptors also exist in thalamus and the cerebral cortex. Consequently, dopamine may also alter thalamocortical activity (Lu et al., 2006). The observed interictal affection of GABA-B mediated inhibitory duration may be related to impaired thalamocortical drive and dysfunctional cortical inhibition previously indicated in migraine patients (Magis et al., 2016, Coppola et al., 2016). We propose that sleep restriction alter an impaired thalamocortical system differently in migraine patients compared to a normal thalamocortical system in controls, causing different effects on cortical inhibition.

Sleep is thought to cause synaptic desaturation which improve signal-to-noise ratio (Kuhn et al., 2016). In healthy subjects, sleep deprivation cause downregulation of dopamine receptors in the striatum accompanied by increased thalamic activity (Volkow et al., 2012, Tomasi et al., 2009). This thalamic upregulation may be to compensate for the worse signal to noise efficiency caused by reduced dopaminergic signalling (Tomasi et al., 2016). The largest migraine genome-wide analysis to date also found enrichment in a single brain region, the nucleus caudatus of striatum (Hautakangas et al., 2022). Furthermore, the familial hemiplegic migraine types 1 and 3 are caused by affection of $Ca_V2.1$ and $Na_V1.1$ channels (Cao and Tsien, 2005, Pietrobon, 2007, Cestele et al., 2013). Dopamine regulates these channels via D1 and D2 receptors in the striatum, altering signals carried by glutamatergic synapses on the GABAergic medium spiny neurons of striatum (Surmeier et al., 2007). In support of altered dopaminergic mechanisms in migraine patients, dopamine D2/D3 receptor availability in the striatum has been observed to be altered during headache and ictal allodynia (DaSilva et al., 2017). Dopamine modulates excitability of thalamic cells and the information integration of thalamocortical systems (Lavin and Grace, 1998). Dopaminergic modulation of

thalamocortical relay neurons is likely relevant for modulation of sensory information. Additionally, trigeminal sensory information mediated via posteromedial nucleus of thalamus to dorsolateral striatum may be under dopaminergic control (Alloway et al., 2017). Dopamine D1 receptors in the ventrobasal thalamus also mediate postsynaptic membrane depolarisation via suppression of barium sensitive inward-rectified K^+ currents, of which ATP-sensitive inward-rectified K^+ channels may be the cause (Govindaiah et al., 2010, Morishige et al., 1993, Kung et al., 2008). These channels are strongly implied in migraine pathogenesis as opening these channels cause migraine attacks in approximately every migraine patient (Al-Karagholi et al., 2017, Al-Karagholi et al., 2019). SUR1-containing ATP-sensitive K^+ channels in the striatum of guinea pigs may also inhibit dopamine release (Avshalumov and Rice, 2003). Interestingly one subtype of these channels termed Kir6.1 is found in distinct areas in the rat brain, like hypothalamic supraoptic nucleus, PVN and striatum (Thomzig et al., 2003). Thus, it is possible that faulty interplay between dopamine receptor types in migraine may cause dysmodulation of inward-rectified K^+ mediated depolarisation in basal ganglia and simultaneously cause sleep related alterations of CSP as seen in this study.

6.1.1 Different pathogenesis may underlie sleep related subgroups of migraine

When differentiating migraine patients by circadian attack onset, the effects of sleep restriction on CSP was only seen for the non-sleep related migraine group (Table 4). Thus, the dopaminergic and GABAergic dysfunction discussed for interictal migraine patients may specifically pertain to the non-sleep related migraine group. As mentioned in the introduction of this thesis, this subgroup may be relatively sleep deprived and show indications of hypoarousability (Engstrom et al., 2013a, Engstrom et al., 2014). This is interesting as the nucleus caudatus of the striatum is shown to be involved in arousal as discussed in the previous section (Stoffers et al., 2014).

In healthy women, estradiol levels after sleep deprivation were positively correlated with slow wave sleep percentage. Estradiol levels were also associated with higher density of dopamine transporters in the striatum. In rats, REM sleep deprivation altered D2 receptor sensitivity in striatum (Martins et al., 2010), and dopamine levels in medial prefrontal cortex and nucleus accumbens were lower during slow-wave sleep than waking and REM- sleep (Lena et al., 2005). Dopamine transporter knockout mice also display increased wakefulness and less slow wave sleep (Wisor et al., 2001). Thus, a dopaminergic dysfunction may cause both relative sleep deprivation and the altered GABAergic inhibition in non-sleep related migraine,

Sleep related migraine subjects displayed a decrease in both LICI and beta-ERS after sleep restriction. Both effects are likely caused by GABAergic inhibition mediated by GABA-B receptors (Muthukumaraswamy et al., 2013, Ziemann et al., 2015). This is similar to the GABA-B mediated CSP reduction observed in non-sleep related migraine. However, there are likely nuances and differences in the GABA-B type inhibition of LICI and ERS, and CSP. The LICI effect is saturated at lower levels of available GABA in the synaptic cleft than CSP and probably represent the magnitude of inhibition wile CSP represent the duration (Ziemann et al., 2015, Benwell et al., 2007, McDonnell et al., 2006). CSP also appear to shorten when LICI increase, indicating different mechanisms which allow one of these inhibitory effects to increase while the other decrease. This may occur due to presynaptic GABA-B mediated autoregulation. A similar discrepancy between CSP and LICI is seen during fatiguing exercise, indicating that CSP and LICI may reflect different neuronal populations (Wu et al., 2000, Benwell et al., 2007). As for CSP, the LICI inhibitory effect decrease throughout the day and may be related to CRH release from the PVN of hypothalamus (Lang et al., 2011). The GABAergic inhibition represented by beta-ERS also represent somatosensory processing from afferent signalling (Cassim et al., 2001, Houdayer et al., 2006). Increased concentrations of GABA are also associated with increased beta-ERS (Gaetz et al., 2011). The GABAergic inhibitory deficit seen in sleep related migraine may consequently involve both GABA-B and be reliant on GABA concentration. Thus, reduced GABA-B inhibition after sleep restriction may be a common mechanism in migraine patients, but with different underlying causes in sleep related subgroups.

Engstrøm et al. have previously observed increased number of awakenings and less slow wave sleep in sleep related migraine (Engstrom et al., 2013a). Increased slow-wave sleep and decreased waking is seen from both GABA-A and GABA-B receptor activation (Gottesmann, 2002). Consequently, we suggest that a GABAergic dysfunction in sleep related migraine may cause disturbed sleep and a susceptibility to dysregulation of cortical excitability and sensory processing from insufficient sleep.

6.1.2 Differentiated effects of insufficient sleep for aura related subgroups

Migraine patients with aura also displayed reduced CSP after sleep restriction compared to controls (Table 4). One study revealed that D2 receptors modulate initiation of CSD in rats indicating a role for D2 antagonism for preventing aura (Haarmann et al., 2014). Consequently, a specific type of dopamine dysfunction may be related to migraine with aura, causing GABAergic dysfunction after insufficient sleep.

Migraine patients without aura had an increase in SICI and a reduction of SAI after sleep restriction. GABA-A mediated inhibition is involved in both SICI and SAI, but the benzodiazepine lorazepam decreases SAI and increase SICI, indicating that different neural circuits are involved in these inhibitory effects (Teo et al., 2009, Ziemann et al., 2015). SICI is likely mediated via α2 and α3 subunits of GABA-A receptors and controlled by presynaptic GABA-B mediated autoinhibition. SAI is probably mediated by α1 subunits of GABA-A receptors and cholinergic input from paramedian thalamic nuclei to the primary motor cortex, possibly modulating basket cells (Ziemann et al., 2015, Florian et al., 2008, Turco et al., 2018). The effect we observed after sleep restriction is similar to the effect induced by the non-selective GABA-A agonist lorazepam. Thus, generally increased GABA-A activity after sleep restriction may explain the effects which we observed in migraine patients without aura.

6.2 Sleep induced changes before attacks may unify hypothalamic dysfunction and thalamocortical dysexcitability

As discussed previously, GABA-B inhibition was reduced by insufficient sleep in sleep related and non-sleep related migraine subjects in the interictal phase. However, GABA-B inhibition expressed as LICI was increased by insufficient sleep closer to the start of the attack and in the preictal phase specifically (Table 5). GABA-B receptor mediated inhibition may be regulated by CRH from PVN of the hypothalamus and decrease during the day. CRH can likely modulate GABAergic neurons postsynaptically in the central nervous system (Lang et al., 2011). Reduced CRH after sleep deprivation has also been suggested to mediate temporary relief of depression observed after sleep deprivation (Vgontzas et al., 1999). CRH also regulate spontaneous waking (Chang and Opp, 2001) and migraine patients are known to display increased sleepiness in the preictal phase preceding an attack (Engstrom et al., 2014). This observation is interesting as the lateral anterior part of hypothalamus, involving the PVN, is activated in the 24-48 hours preceding a migraine attack (Schulte and May, 2016, Schulte et al., 2020b, Schulte and Peng, 2019). PVN also control yawning, a common premonitory symptom which may be induced by activating oxytocinergic neurons from PVN to ventral tegmental area, hippocampus, and amygdala (Sanna et al., 2012, Guven et al., 2018, Argiolas and Melis, 1998). This happens in parallel to an increase of extracellular dopamine in the shell of nucleus accumbens, which may arise from the dorsal raphe nucleus of pons (Hasue and Shammah-Lagnado, 2002). Remarkably, this activation pattern resembles the report by Schulte at al. that functional connectivity is enhanced between nucleus

accumbens, dorsal pons (probably including dorsal raphe nucleus), left amygdala and hippocampus in the preictal phase (Schulte et al., 2020b).

GABA-containing axon terminals in dorsal raphe is also innervated by CRH-expressing neurons (Hauger et al., 2006), and dopaminergic innervation may regulate CRH neurons of PVN (Eaton et al., 1996). PVN neurons controlling trigeminovascular neurons have previously been suggested to modulate or trigger migraine (Robert et al., 2013). Interestingly, oxytocin have been observed to prevent migraine attacks and to be related to estrogen and estrogen-drops triggering migraine (Krause et al., 2021). Oxytocin is also capable of modulating CRH neuron excitability in the PVN (Jamieson et al., 2017). CRH release is also modulated by orexins (Schulte and Peng, 2019) and by vasopressin from suprachiasmatic nuclei (Oster et al., 2017). Higher levels of CRH and orexin-A in cerebrospinal fluid have been associated with chronification of migraine (Sarchielli et al., 2008) and vasopressin has been implied in migraine pathophysiology (Gupta, 1997). Nitric oxide (NO) is also involved in the control of yawning in PVN (Melis and Argiolas, 1999), and NO donors is a well-known trigger of migraine (Neeb and Reuter, 2007) and premonitory symptoms (Afridi et al., 2004). Taken together, altered preictal LICI may represent a dysfunctional preictal cortical inhibitory capability. We suggest that this finding is both related to previously described inhibitory dysfunction of the preictal phase and altered preictal activity of hypothalamus as elaborated on in section 1.3.1. We hypothesise that preictal cortical dysexcitability in migraine originate from disturbed function of the hypothalamus which is vulnerable to dysregulation from changes in sleep.

The observed decrease of SAI by sleep restriction closer to the start of an attack (Table 5) may indicate cholinergic dysfunction affecting α1 GABA-A mediated inhibition. REM density has also been shown to be reduced in the preictal phase of migraine. This finding indicate a cerebral cholinergic input deficit during sleep before migraine attacks (Goder et al., 2001). Reduced levels of cortical acetylcholine have also been observed in healthy subjects after sleep deprivation (Boonstra et al., 2007). Hence, cholinergic systems may become dysfunctional before the start of a migraine attack, causing altered sleep architecture and a susceptibility to altered GABA-A mediated inhibition from insufficient sleep. Interestingly, the Kir6.1 channel implied in migraine pathophysiology is located in cholinergic interneurons of the striatum and the present results indicate a role for striatum in migraine pathogenesis (Thomzig et al., 2003).

6.3 Increased need for sufficient sleep during migraine attacks

We observed gradual changes in the effect of insufficient sleep after resolution of migraine attacks. SICI and beta-ERS was more reduced and beta-ERD more increased after sleep restriction the shorter time that had elapsed since the resolution of the migraine headache attack. For the 24-hour postictal phase specifically, SICI was more reduced and ICF more increased by sleep restriction (Table 5). Reduced SICI and increased ICF is also observed after total sleep deprivation in healthy subjects and accompany alterations in neuroplasticity and compromised learning, memory, and attention (Salehinejad et al., 2022). This effect may be related to lack of synaptic desaturation and generally reduced signal-to-noise ratio (Kuhn et al., 2016, Salehinejad et al., 2022). Increased beta-ERD during motor imagery is associated with reduced SICI, which corresponds with our observation and indicate a GABA-A related mechanism of the increased beta-ERD (Takemi et al., 2013). As the sleep restriction before examinations in the postictal phase occurred during attacks, we suggest that migraine patients are more vulnerable to sleep reduction during attacks and may have greater need for sufficient sleep during attacks to maintain normal neurological capacity after attack resolution. We suggest that this finding may represent a physiological basis for the frequently observed need to sleep during attacks for migraine patients (Kelman and Rains, 2005) and that maintaining sufficient sleep during attacks may be a reasonable advice to give to migraine patients to improve postictal functioning.

The simultaneously reduced beta-ERS after sleep restriction (Table 5) may indicate that it is the GABA concentration that is altered. Concentration of GABA is important for motor learning and synaptic strengthening. Synaptic strength is suggested to be saturated during wake and restored by sleep (Salehinejad et al., 2022, Kolasinski et al., 2019). Thus, we hypothesise that dysregulated synaptic strength and reduced signal-to-noise ratio may be related to symptoms of the postictal phase. This hypothesis should be further investigated by evaluating the effect of sleep during attacks on postictal symptoms and function.

6.4 Suggested pathway for future studies in migraine

The migraine diagnosis allows for wide variation in clinical presentation. We suggest continuing to explore subgroupings of migraine patients by phenotype in an attempt to discover subtypes of migraine affected by different pathophysiological mechanisms. Such subgroups may consequently require different treatment. Conflicting results in investigations into the complete migraine group may be caused by combinations of what is different subtypes of the migraine diagnosis. As displayed in this study, subgrouping migraine patients

by sleep or non-sleep related attack onset may represent different pathophysiological entities and this subgrouping should be implemented in future studies.

Sleep restriction prove to be a feasible and interesting method to apply in migraine research. The connection between migraine and sleep is one of the most widely recognised parts of the migraine clinical presentation. Further investigations into circadian rhythm related mechanisms in migraine should be conducted as these appear closely connected to migraine pathogenesis. However, evaluating effects of sleep changes in the same subject during the different migraine phases is challenging as demonstrated in this study. Increased number of examinations with different sleep conditions or utilising subjects with predictable attacks could improve the strength of such analyses.

TMS is a technique with several possibilities for investigating central nervous characteristics in humans. Combining TMS with other examination modalities may allow for simultaneous investigation of different parts of the nervous system. TMS may be combined with high density EEG to investigate cortical responses to magnetic perturbation with high temporal resolution and possibility of source localisation. TMS and EEG may also be combined with MRI to allow for high spatial resolution. Because the mechanisms suggested to be part of migraine pathophysiology in this thesis involves large networks and complex interactions, the possible causes of migraine may originate in different parts of these systems and differ between migraine patients. Thus, we suggest that these mechanisms should be investigated further in longitudinal studies with subjects as their own controls. Such investigations should be conducted with repeated measures during the same migraine cycle. Investigations of cortical mechanisms necessary to experience migraine symptoms should be combined with evaluation of dopaminergic, GABAergic and glutamatergic properties in each individual and supplemented with imaging modalities capable of mapping neurotransmitter concentration and effects such as magnetic resonance spectroscopy and PET. The challenge of finding reliable biomarkers for each individual in the heterogeneous migraine group may be improved on by combining measurements of “omics” and functional measures such as TMS-EEG to detect meaningful correlations in the individual, related to the suggested pathways.

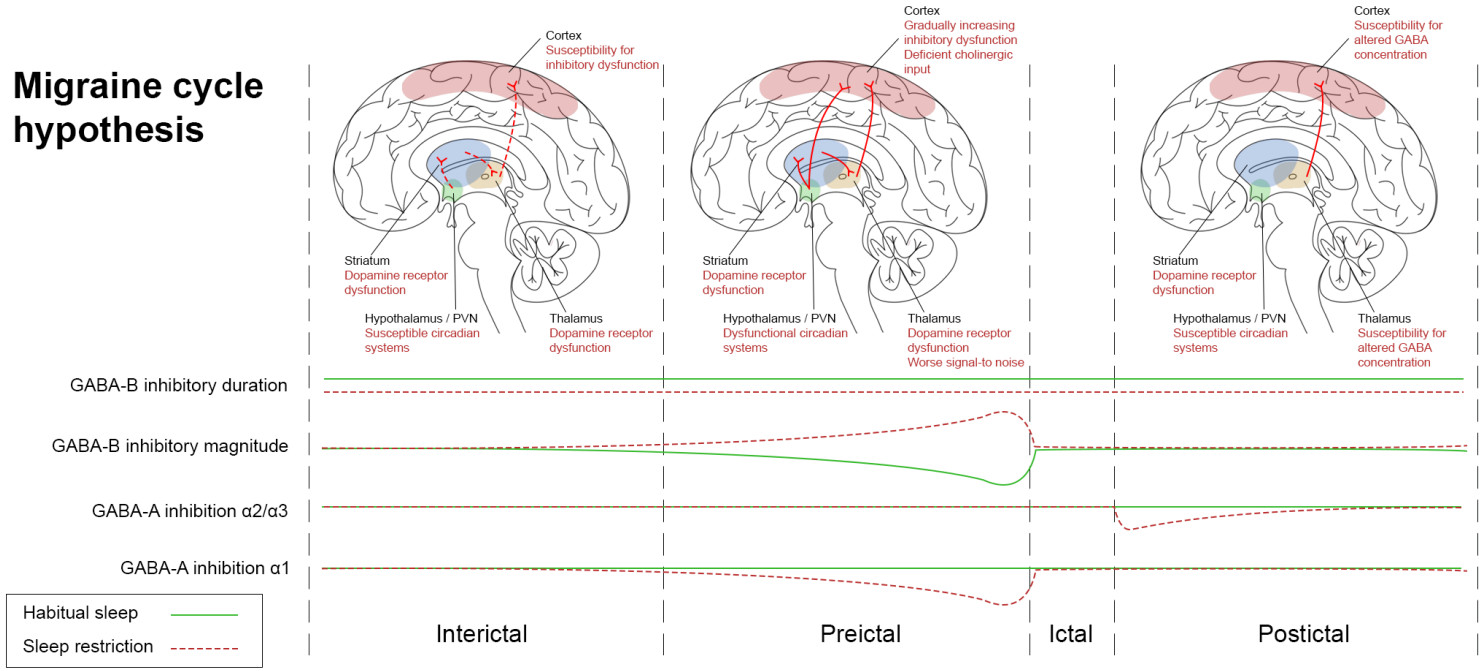

Figure 6 Migraine cycle hypothesis

Schematic illustration of central nervous mechanisms hypothesised to be of importance for the connection between the migraine cycle and sleep. Anatomical illustrations indicate areas which may be affected by the migraine disease during different stages of the migraine cycle. Specific systems and transmitters hypothesised to be involved are described in red text. The interictal migraine brain is hypothesised to encompass dopaminergic dysfunction of subcortical structures including the striatum and thalamus, a circadian system susceptible to dysregulation from certain input like insufficient sleep and a cortex with susceptibility for the occurrence of altered inhibitory function. The preictal migraine brain is hypothesised to be further affected by the subcortical dopaminergic dysfunction which may participate in causing inhibitory dysfunction of the cortex, possibly related to a dysregulated circadian system. The postictal migraine brain is hypothesised to involve a susceptibility to dysfunction of another type of a sleep dependent inhibitory system, possibly closely

related to GABA concentration. The lines representing increases and decreases in inhibitory function are of an illustrative nature. Illustration of GABA-B inhibitory duration is based on the interictal effects of sleep restriction seen on cortical silent period (CSP) which were not further altered in the different migraine phases (Paper I, II). This inhibitory property is likely dependent on dopaminergic mechanisms and hypothalamus/PVN circadian function. The depiction of altered GABA-B inhibitory magnitude is based on the effects seen on long interval intracortical inhibition (LICI) towards the commencement of attacks (Paper II). LICI was reduced preictally in a small preictal sample but increased by sleep restriction compared to the decreased inhibition seen after habitual sleep. This was interpreted as cortical GABAergic dysfunction dependent on the control of circadian systems. Furthermore, reduced GABA-A inhibition from α2/α3 subunits after the end of attacks is a finding interpreted from alterations of short interval intracortical inhibition (SICI) and intracortical facilitation (ICF) (Paper II). These inhibitory properties are also dependent on dopaminergic mechanisms. However, supporting results from event related desynchronisation/synchronisation (ERD/ERS) may also indicate that altered GABA concentration may be causing this effect (Paper III). GABA-A inhibition from α1 subunits was reduced by sleep restriction before commencement of attacks and may be related to deficient cholinergic input in the preictal phase. This interpretation is based on effects found on short latency afferent inhibition (SAI). The model in whole depicts a cortical inhibitory system susceptible to alterations from underlying dysfunctions in dopaminergic modulation and circadian systems of migraine patients. Results in the preictal and postictal phase are based on a small sample size and the suggested mechanisms need confirmation in larger studies of investigations into the specific mechanisms.

7. Conclusion

We have conducted a randomised, blinded crossover study of migraine subjects and healthy controls undergoing both restricted and habitual sleep. We have utilised TMS- and EEG-based measurements to evaluate effects of sleep changes on cortical excitability in migraine subjects both compared to controls, throughout the migraine cycle, and between migraine subgroups. Interictally, we detected reduced CSP, representing inhibitory GABA-B effects, after sleep restriction in the migraine group and non-sleep related subgroup. In sleep related migraine, other representations of GABA-B inhibition in form of LICI and beta-ERS were reduced by sleep restriction interictally. The effects on CSP correlated with degree of ictal symptoms of hypersensitivity and premonitory dopaminergic symptoms. We also detected further alterations of LICI before attacks and reduced inhibition in form of reduced SICI and beta-ERS and increased beta-ERD after sleep restriction after attacks.

We have revealed a possible connection between a dysregulated inhibitory system in migraine and subcortical brain regions related to control of sleep and wake. Sleep restriction induced effects on cortical GABA-B mediated inhibition which differed between sleep related migraine subgroups. This type of inhibition is likely dependent on circadian control in the hypothalamus and PVN. Migraine subjects may also have an impaired thalamocortical system due to dopaminergic dysregulation which is abnormally affected by insufficient sleep. We hypothesise that migraine pathophysiology encompasses a dysfunctional inhibitory system modulated by hypothalamic and dopaminergic mechanisms.

We also observed gradual changes in effects of insufficient sleep on cortical inhibitory systems towards the commencement of an attack. GABAergic systems were differently affected by sleep changes the shorter time that remain until attack start. Thus, we hypothesise that hypothalamic and dopaminergic modulation of cortical inhibition is further altered as a part of the preictal changes precipitating an attack.

Closely following a migraine attack, we observed changes in GABAergic inhibition after sleep restriction which resemble the effect seen after total sleep deprivation in healthy subjects. This finding may indicate that migraine patients are vulnerable to reduced sleep during attacks and consequently have increased need for sufficient sleep during attacks to maintain normal neurological function, synaptic saturation, and cerebral signal-to-noise ratio postictally.

We suggest that the proposed mechanisms should be further investigated in longitudinal studies combining measurements of dopaminergic, GABAergic and glutamatergic properties, imaging of neurotransmitter dynamics and simultaneous mapping of cortical function necessary to experience migraine symptoms.

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Sleep restriction alters cortical inhibition in migraine: A transcranial magnetic stimulation study

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HIGHLIGHTS

- Reduced sleep alters central nervous inhibition from GABAergic and dopaminergic mechanisms differently in migraineurs and controls.
- Central nervous inhibition is differently affected by sleep changes in non-sleep related and sleep related migraine.
- Identifying sleep related subgroups of migraineurs could have implications for differentiated GABA or dopamine targeted treatment.

ABSTRACT

Objective: Migraine is a primary headache disorder with a well-known association with insufficient sleep. However, both the underlying pathophysiology of the disease and the relationship with sleep is still unexplained. In this study, we apply transcranial magnetic stimulation to investigate possible mechanisms of insufficient sleep in migraine.
Methods: We used a randomised, blinded crossover design to examine 46 subjects with migraine during the interictal period and 29 healthy controls. Each subject underwent recordings of cortical silent period, short- and long-interval intracortical inhibition, intracortical facilitation and short-latency afferent inhibition after both two nights of habitual eight-hour sleep and two nights of restricted four-hour sleep.
Results: We found reduced cortical silent period duration after sleep restriction in interictal migraineurs compared to controls ($p = 0.046$). This effect was more pronounced for non-sleep related migraine ($p = 0.002$) and migraine with aura ($p = 0.017$). The sleep restriction effect was associated with ictal symptoms of hypersensitivity such as photophobia ($p = 0.017$) and overall silent period was associated with premonitory dopaminergic symptoms such as yawning ($p = 0.034$).
Conclusions: Sleep restriction reduces GABAergic cortical inhibition during the interictal period in individuals with migraine.
Significance: Sleep related mechanisms appear to affect the pathophysiology of migraine and may differentiate between migraine subgroups.

Abbreviations: CS, Conditioning stimulus; CSP, Cortical silent period; EMG, Electromyography; ICF, Intracortical facilitation; ISI, Interstimulus interval; LICI, Long-interval intracortical inhibition; MA, Migraine with aura; MEP, Motor evoked potential; MwoA, Migraine without aura; NSM, Non-sleep related migraine; PAG, Periaqueductal gray matter; ppTMS, Paired pulse transcranial magnetic stimulation; REM, Rapid eye movement sleep; RMT, Resting motor threshold; rTMS, Repetitive transcranial magnetic stimulation; SAI, Short-latency afferent inhibition; SICI, Short-interval intracortical inhibition; SM, Sleep related migraine; SR, Sleep restriction; TMS, Transcranial magnetic stimulation; TS, Test stimulus.

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1. Introduction

Migraine is a primary headache disorder characterised by recurrent attacks of headache associated with a wide spectrum of other symptoms both preceding, accompanying and following the headache attack (Karsan et al., 2018, Karsan et al., 2021). The disease affects about 15% of adults aged 15–64 globally (Steiner et al., 2021), making it the leading cause for years lived with disability below 50 years of age (Steiner et al., 2018).

Despite the large impact of migraine, the underlying disease mechanisms remains to be fully elucidated. Migraine is currently understood as a disease where neuronal dysexcitability and abnormal brain network connectivity fluctuates between the different migraine phases (Cosentino et al., 2014b, Mykland et al., 2019, Barbanti et al., 2020b, Peng and May, 2019). Results from daily functional magnetic resonance imaging studies implicate altered hypothalamic function and changes in connectivity of dopaminergic centres as important for migraine attack generation (Schulte and May, 2016, Schulte et al., 2020). Furthermore, cortical dysexcitability may explain increased sensitivity to external stimuli in migraineurs (Coppola et al., 2007). Observed reductions in interictal silent periods induced by transcranial magnetic stimulation (TMS) (Curra et al., 2007, Maier et al., 2011) suggest that dysfunctional thalamocortical loops may reduce cortical inhibition in people with migraine. Additionally, reduced lateral inhibition interictally has also been measured by somatosensory evoked potentials (Coppola et al., 2016), and repetitive TMS (rTMS) findings suggest low thresholds for inducing inhibitory responses interictally in migraineurs (Cosentino et al., 2018, Brighinal et al., 2011, Cosentino et al., 2014a). However, many previous findings of brain dysexcitability in migraine are seemingly contradictory, reflecting different facets of a complex underlying pathophysiology that remains to be fully understood (Cosentino et al., 2014b).

People with migraine commonly report sleep complaints, describe headaches upon awakening and use sleep as an approach to abort headache (Kelman and Rains, 2005, Ødegård et al., 2010). Migraineurs also describe worse sleep quality than healthy individuals and having insomnia-like sleep patterns (Stanyer et al., 2021, Kelman and Rains, 2005, Kim et al., 2018). Furthermore, a bidirectional risk-relationship between insomnia and migraine has been found in large epidemiological studies (Odegard et al., 2011, Odegard et al., 2013). Several anatomical localisations and pathways believed to be involved in migraine pathogenesis, do overlap with systems of sleep physiology (Vgontzas and Pavlović, 2018, Tiseo et al., 2020). These include parts of the cortical default mode network (Chou et al., 2021), hypothalamus (Saper et al., 2005, Schulte and May, 2016), thalamus, locus coeruleus, dorsal raphe and periaqueductal gray matter (PAG). These structures are depicted in Fig. 1 in Tiseo et al. (2020), and are involved in both pain control, reduced interictal serotonin in migraine (Vgontzas and Pavlović, 2018), migraine attack generation (May, 2017) and sleep control. Lastly, dopaminergic systems are important for both arousal and premonitory yawning and mood changes in migraine (Vgontzas and Pavlović, 2018). In addition, several sleep traits have genetic overlap with migraine (Daghlas et al., 2020) and various neurotransmitters with suggested roles in migraine pathophysiology are also involved in the processes of maintaining wakefulness (Scammell et al., 2017, Goadsby and Holland, 2019). Thus, unravelling the relationship between sleep and migraine appear to be central to expand our understanding of both the pathophysiology of migraine and the everyday management of the disease for migraine patients.

Sleep restriction (SR), allowing about 50% sleep for two nights (Matre et al., 2015, Hansen et al., 2021), is a human experimental model of insufficient sleep. Sleep deprivation in healthy subjects may alter cortical inhibitory and facilitatory systems (Huber et al., 2013, Civardi et al., 2001), and SR seems to increase pain sensitivity in healthy subjects (Matre et al., 2015). Increased pain sensitivity has previously been discovered in migraine (Uglem et al., 2017, Sand et al., 2008), and may be linked both to increased homeostatic sleep pressure (Borbély, 1982) caused by increased sleep need in migraine (Engstrøm et al., 2013) and reduced intracortical inhibition (Uglem et al., 2016). In a recent publication, we found that pressure pain sensitivity tended to increase after SR in interictal migraineurs (Neverdahl et al., 2021).

TMS is suitable for investigating inhibitory/excitatory function of cortical networks (Rossini et al., 2015). Relevant aspects of inhibitory/excitatory systems of the central nervous system can be studied by cortical silent period (CSP) duration, the paired pulse TMS (ppTMS) subtypes of intracortical facilitation (ICF), short- and long-interval intracortical inhibition (SICI and LICI) and short-latency afferent inhibition (SAI). CSP reflect intensity dependent activity of GABA-A and GABA-B-receptors (Ziemann et al., 2015, Hupfeld et al., 2020). ICF is probably influenced both by excitatory NMDA receptors and inhibitory GABA-A receptors, while SICI reflect GABA-A receptor mediated inhibitory postsynaptic potentials and LICI likely represent GABA-B mediated inhibition (Ziemann et al., 2015). SAI seems to reflect central cholinergic activity modified by a GABA-A type of inhibition (Turco et al., 2018). Since these TMS-measures reflect different parts of glutamatergic, cholinergic and GABAergic activity, which also is under influence of e.g., dopaminergic and noradrenergic transmitter systems (Ziemann et al., 2015, Cosentino et al., 2018), a study of all measures may detect how neuronal and synaptic physiology is affected in migraine.

The selected TMS techniques evaluate transmitter systems already implied in migraine pathophysiology. Altered GABA metabolism have been suggested in migraine (Aguila et al., 2015) and may be associated with central sensitization (Aguila et al., 2016). Glutamatergic dysfunction has been suggested from findings with various methods (Cosentino et al., 2014c). Dopamine also mediate several migraine symptoms (Barbanti et al., 2020a) and dopaminergic centres seem directly involved in migraine generation (Schulte et al., 2020). The connection between cortical and hypothalamic function in migraine may also be investigated by CSP and LICI, as these responses are likely modulated by hypothalamic control of circadian rhythm (Lang et al., 2011). The results of previous studies with these TMS-measurements have been inconsistent. Some studies have reported reduced CSP or SICI in interictal migraineurs (Khedr et al., 2006, Curra et al., 2007, Brighina et al., 2005, Neverdahl et al., 2017, Brighina et al., 2009a), while other studies have not confirmed these findings (Áfra et al., 1998, Siniatchkin et al., 2007). Increased ICF in interictal migraine was seen in one study (Cosentino et al., 2018), but not in others (Brighina et al., 2005, Áfra et al., 1998). Although more scarcely investigated, LICI was similar to controls in one study (Siniatchkin et al., 2007), and SAI was reduced interictally (Coppola et al., 2020). Hence, a comprehensive study of several TMS measures in one well-characterized migraine group may provide more detail to the role of these transmitter systems and contribute to the clarification of reported inconsistencies.

A migraine attack may be a final common pathway for different underlying abnormalities that may differ between migraine subgroups (Cutrer, 2010). One differentiation between subtypes of migraine patients is into the groups of migraine with aura (MA) and migraine without aura (MwoA). The migraine aura is defined as fully reversible and gradually spreading neurological symptoms thought to be caused by cortical spreading depression (Coppola

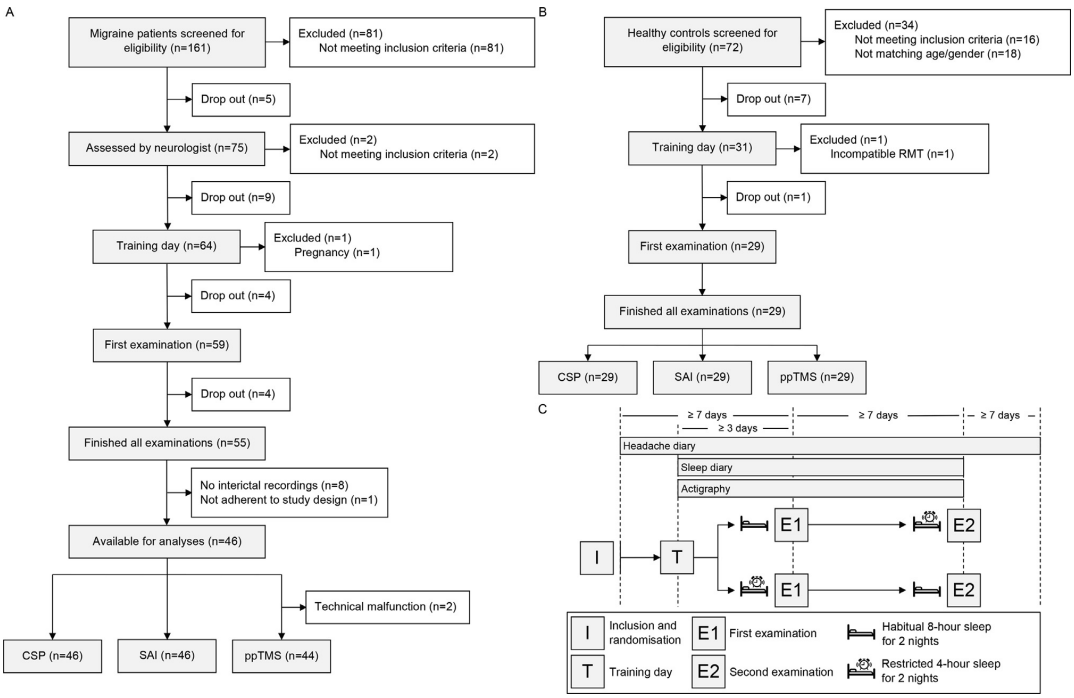

Fig. 1. Study design and inclusion. Flow chart for the participant inclusion process for (**A**) migraine subjects and (**B**) healthy controls, reporting number of participants (n) for each step. (**C**) Overview of the study design which was equal for migraine subjects and controls. Participants were randomised for order of sleep conditions with block randomisation to ensure equal distribution. Interictal recordings were determined by a 24-h cut off from the reported start or end of migraine attack pain. CSP, Cortical silent period; SAI, Short-latency afferent inhibition; ppTMS, paired pulse Transcranial magnetic stimulation; I, Inclusion and randomisation; T, Training day; E1, First examination; E2, Second examination.

et al., 2019, IHS, 2018). One recent review also concludes that electrophysiological abnormalities in migraineurs were more frequently present and had greater amplitude in migraineurs with aura (Coppola et al., 2019). However, too little is known about the effect of insufficient sleep in the subgroups of MA and MwoA. Lateef et al. (Lateef et al., 2011) found similar prevalence of disordered sleep in these subgroups in adults, while MA reported more sleep problems than MwoA among adolescents in another study (Lateef et al., 2019).

We have in a previous study investigated a sleep related subgrouping of migraine subjects; namely those having attack onset mostly during sleep, sleep related migraine (SM), and subjects with non-sleep related migraine (NSM). These two groups differ in objective measures of sleep quality. NSM-subjects had increased amount of N3 slow wave sleep defined using polysomnography (Iber et al., 2007) and reduced thermal pain thresholds, indicating that a relative sleep deficit, in spite of no foregoing sleep deprivation, may be associated with facilitation of pain transmission (Engstrøm et al., 2014). In a recent publication, we found that heat pain sensitivity also tended to increase after SR in SM-subjects (Neverdahl et al., 2021).

We hypothesised that migraineurs have an underlying interictal dysfunction of sleep-wake regulating brain systems which influence thalamocortical systems regulating cortical excitability. We propose that sleep restriction consequently will induce more prominent changes in inhibitory and/or facilitatory systems in migraine subjects compared to controls. Our primary objective was to investigate whether CSP duration, SICI and ICF is affected differently by sleep restriction in interictal migraineurs and controls. These TMS-measures have been most frequently investigated in migraine subjects, by others and ourselves (Neverdahl et al., 2017), and may be especially relevant because of the proposed dysfunction of thalamocortical inhibitory regulation in migraine. Previous results with these TMS measures should also be independently confirmed. Secondary objectives were to explore the effect of sleep restriction on additional TMS measures with plausible roles in migraine (LICI, SAI) and to compare the effect of sleep restriction on all TMS measures in migraine subgroups (NSM/SM and MwoA/MA). Finally, we examined whether findings in the investigated inhibitory and facilitatory systems were related to certain clinical characteristics of migraine by performing explorative analyses on the effect of clinical migraine variables on TMS responses. To our knowledge, we are the first to report results of TMS-measurements in migraine after both habitual sleep and sleep restriction.

2. Methods

2.1. Subjects

We recruited episodic migraine subjects and healthy controls through newspapers, radio, television, and social media. All subjects were screened by nurses experienced in headache research using a predefined inclusion/exclusion-form. Episodic migraine subjects were evaluated by a neurologist for inclusion using predefined inclusion/exclusion criteria, which included a diagnosis of migraine with and/or without aura according to The International

Classification of Headache Disorders, 3rd edition (IHS, 2018). Inclusion criteria restricted migraineurs to have between one and six self-reported attacks per month for the last six months. All subjects were between 18 and 65 years old, living with less than 1.5 h driving time from the hospital. Migraine subjects were not allowed to use prophylactic treatment during the study period or at least four weeks before the first examination. Migraine subjects with tension type headache for seven days or more per month, or significant comorbid headache like cluster headache or hypnic headache were excluded. Controls were excluded if they reported to have headache described as painful one day per month or more, had previously consulted a doctor about headache described as painful, or usually used medications for headache described as painful. Migraine subjects and controls with known sleep disorders, regular sleep need < 6 h during both weekdays and weekends/vacations, treated hypertension or blood pressure > 160/110 mmHg, infectious, metabolic, endocrine, neuromuscular or connective tissue disease, other acute or chronic painful diseases, recent injury, symptomatic heart disease, lung disease affecting function, cerebrovascular disease, neurological or psychiatric disease affecting function, epilepsy in close relatives, neoplastic disease, treatment with neuroleptics, antiepileptic drugs, antidepressants or other medications affecting neural, vascular or muscular function, pregnancy, previous craniotomy, alcohol or narcotics abuse, prophylactic allergy treatment, or contraindications for TMS (epilepsy, pregnancy or relevant implants) were also excluded. Participants were asked not to exercise, consume caffeinated beverages, or use or smoke tobacco on the same day as the examinations.

Demographic data were recorded using a questionnaire and a semi-structured interview. We also collected information regarding headache characteristics and accompanying symptoms in a questionnaire. Among these were a Norwegian translation of the 12-item Allodynia Symptom Checklist (ASC-12) (Lipton et al., 2008).

A headache nurse screened 72 healthy controls and 161 migraine subjects for eligibility. Further details on exclusion and drop out is described in Fig. 1.A and 1.B. We used a 24-h cut off for interictal migraine as used in a previous TMS study by our group, defining the interictal phase as lasting from 24 h after resolution of pain until 24 h before pain onset (Neverdahl et al., 2017). Migraine subjects with at least one interictal recording were included in the analysis, which excluded 8 migraine participants. One interictal migraine subject was not adherent to the sleep instructions and was therefore excluded. One control subject had a resting motor threshold (RMT) during TMS of 96% of the maximal stimulator output and accordingly none of the TMS measurements in this study were possible to perform for this subject as they require stimulations of 120% RMT. Two interictal migraine subjects had no ppTMS recordings due to a technical malfunction of the coil thermostat making the stimulator not able to execute paired pulse stimulations. In the end, 46 migraine subjects were available for interictal CSP and SAI analyses, 44 migraine subjects for ppTMS analyses and 29 controls for CSP, ppTMS and SAI analyses. Demographic data for both groups are presented in Table 1.

The study was approved by the Regional Committee for Medical Research Ethics Central Norway. Written, informed consent was obtained from all subjects. All participants were remunerated with 900 NOK intended to cover expenses (about 90 EUR with current exchange rates).

2.2. Study design

The crossover study design is illustrated in Fig. 1.C. All participants underwent TMS at three different days. The first training day was arranged for the subjects to become familiar with all examinations. They also received instructions on filling out a sleep diary and training in using a wrist-worn actigraph (Actiwatch Spectrum, Philips Norge AS, Oslo, Norway) to register sleep data from the first training day until the second examination day. Thus, we measured sleep duration with actigraphy and sleep diary each night from the first training day until the second examination day in every subject. The same examinations which were prepared on the training day were performed on the first and second examination day, preceded by either two nights of 8-h sleep or two nights of 4-h sleep with wake-up-time about 7:00 am (Fig. 1.C). The order of sleep conditions was randomised and counterbalanced for migraine subjects and controls separately.

The two examination days were separated by at least seven days. Each examination was either scheduled for 08:00 am or 10:30 am, the same time for each examination for the same subject. The different starting times were equally distributed among migraine subjects and controls. Each examination lasted about two hours, which also included electroencephalography and quantitative sensory testing not yet reported.

Migraine subjects continuously filled in a headache diary from at least one week before examinations, until at least one week after examinations. Diaries were the same as in previous studies by our group (Neverdahl et al., 2021).

All examinations and data analyses were performed by the same investigator, who was blinded for diagnosis and sleep condition.

2.3. Transcranial magnetic stimulation

2.3.1. Equipment

Subjects were seated comfortably in a chair with both forearms resting on a pillow during examinations. TMS was performed using a figure-of-eight MCF-B65 Butterfly Coil (MagVenture A/S, Farum, Denmark) with biphasic 280 μs pulse over the left hemisphere, initially inducing anteroposterior current in the tissue. The coil was connected to a MagPro X100 stimulator with MagOption (MagVenture A/S, Farum, Denmark). We have previously used biphasic waveforms instead of conventional monophasic posteroanterior stimulation in another study of TMS responses in migraine (Neverdahl et al., 2017). This decision is based on several recent observations. SICI do mainly affect the late I-waves and consequently the anteroposterior current direction which mainly elicit these I-waves is of interest to include in the simulation (Wessel et al., 2019). SICI and ICF measurements have been shown to be comparable between monophasic and biphasic stimulation waveforms and between anteroposterior and posteroanterior current directions (Wessel et al., 2019). ICF has also been shown to be more reliable with biphasic pulses and LICI to be more reliable with anteroposterior direction than posteroanterior (Davila-Pérez et al., 2018). Monophasic posteroanterior current has also been shown to not elicit significant ICF (Davila-Pérez et al., 2018). Regarding CSP duration, the reduced RMT one may expect from biphasic stimulation should not influence CSP results (Davila-Pérez et al., 2018). Thus, we evaluated biphasic stimulations as suited for the intended investigations in migraineurs. Localite TMS Navigator (Localite GmbH, Bonn, Germany) was used for keeping the coil steady at the determined location. Electromyography (EMG) from the abductor pollicis brevis muscle were recorded using Ag/AgCl electrodes and a Dual Bio Amp (ADInstruments, Dunedin, New Zealand) connected to a PowerLab 8/35 (ADInstruments, Dunedin, New Zealand). LabChart software version 8 (ADInstruments, Dunedin, New Zealand) with Sampling rate 10 kHz, high pass 1 Hz and low pass 2 kHz were used to record EMG and to trigger the MagPro stimulator for RMT, CSP and SAI measurements. The ppTMS protocol was directly triggered by the X100 stimulator. A Digitimer Constant Current Stimulator model

Table 1
Demographic and clinical data on migraine subjects with at least one interictal recording, and controls.

	Interictal migraine (*n = 46*)	Controls (*n = 29*)	Non-sleep related migraine (*n = 32*)	Sleep related migraine (*n = 14*)	Migraine without aura (*n = 27*)	Migraine with aura (*n = 19*)
Women/men	41/5	22/7	31/1	10/4	24/3	17/2
Age (years)	37.5 (11.2)	36.9 (12.1)	35.6 (10.1)	42.0 (12.6)	37.0 (12.0)	38.3 (10.1)
Right-/left-handedness[a]	42/4	26/3	29/3	13/1	25/2	17/2
MwoA/MA	27/19		18/14	9/5		
NSM/SM	32/14				18/9	14/5
Allodynia score (0–24)[b]	4.7 (4.6)		4.6 (4.9)	5.0 (4.1)	4.4 (4.5)	5.2 (4.8)
Migraine usual duration (hours)	21.6 (22.1)		24.5 (23.7)	15.0 (16.7)	25.2 (25.1)	16.6 (16.2)
Migraine attacks/month last 6 months (1–4)[c]	2.2 (0.4)		2.2 (0.4)	2.3 (0.5)	2.1 (0.4)	2.3 (0.5)
Migraine usual intensity (1–4)[d]	2.6 (0.5)		2.6 (0.5)	2.5 (0.5)	2.6 (0.5)	2.5 (0.5)
Headache history (years)	21.4 (11.6)		21.0 (11.8)	22.3 (11.4)	20.9 (11.4)	22.1 (12.2)
Photophobia (0–3)[e]	2.5 (0.7)		2.7 (0.5)	2.1 (0.8)	2.4 (0.8)	2.7 (0.5)
Phonophobia (0–3)[e]	2.2 (0.9)		2.4 (0.8)	1.6 (0.7)	2.2 (0.9)	2.2 (0.8)
Osmophobia (0–3)[e]	1.6 (1.2)		1.8 (1.2)	1.1 (1.2)	1.4 (1.3)	1.8 (1.1)
Premonitory yawning (yes/no)[f]	11/35		8/24	3/11	7/20	4/15
Premonitory mood change (yes/no)[f]	14/32		11/21	3/11	8/19	6/13
Sleep time (habitual) (min)[g]	452.9 (35.8)	456.4 (30.8)	455.2 (32.4)	448.0 (43.6)	459.1 (32.6)	445.5 (39.0)
Sleep time (restricted) (min)[g]	258.8 (41.5)	246.9 (23.5)	256.2 (38.6)	263.9 (48.3)	260.7 (41.7)	255.8 (42.6)
Days since last menstruation start (habitual sleep)[h]	13.1 (9.1)	11.6 (7.3)	13.7 (9.4)	11.2 (9.0)	10.4 (9.1)	16.1 (8.6)
Days since last menstruation start (restricted sleep)[h]	13.9 (7.3)	20.2 (10.6)	14.0 (8.1)	13.8 (3.8)	14.0 (7.7)	13.9 (7.2)
Resting motor threshold (habitual sleep)	56.2 (9.0)	54.6 (6.8)	56.5 (8.5)	55.5 (10.4)	57.0 (9.2)	55.3 (9.0)
Resting motor threshold (restricted sleep)	56.4 (8.3)	54.8 (6.7)	57.6 (9.5)	53.9 (4.7)	57.9 (8.5)	54.2 (7.9)

The table displays mean (SD) or number of participants. MwoA = Migraine without aura; MA = Migraine with aura; NSM = Non-sleep related migraine; SM = Sleep related migraine. Interictal cut-off is 24 h.

[a] Self reported preferential use of one hand.

[b] Allodynia score (ASC-12) during usual migraine attacks.

[c] Categories: 1 = less than 1 per month, 2 = 1–3 per month, 3 = 4–5 per month, 4 = 6 or more per month. (Category 2, *n* = 37; category 3, *n* = 9).

[d] Categories: 1 = light – can keep doing a task, 2 = moderate – can do light tasks, 3 = strong – have to lie down, 4 = extremely strong – cannot lay still. (Category 2, *n* = 20; category 3, *n* = 26).

[e] Symptom in migraine attacks not medically treated: 0 = no symptom, 1 = to a small degree, 2 = to a medium degree, 3 = to a strong degree. (Photophobia 1*n* = 4, 2*n* = 13, 3*n* = 29; Phonophobia 0*n* = 2, 1*n* = 7, 2*n* = 18, 3*n* = 19; Osmophobia 0*n* = 13, 1*n* = 9, 2*n* = 9, 3*n* = 15).

[f] Reporting premonitory symptom in any percentage of attacks.

[g] Mean sleep time for the two sleep-controlled nights for each sleep condition.

[h] Include interictal female migraineurs with menstruations after habitual (n = 21) and restricted (n = 19) sleep, and female controls with menstruations after habitual (n = 11) and restricted (n = 13) sleep. Examinations performed with days from last menstruation above 35 were excluded (n = 6 examinations, range 41–90 days) to eliminate abnormal menstrual cycles.

DS7A (Digitimer, Welwyn Garden City, United Kingdom) was used for stimulation of the median nerve during measurements of SAI, using 200 μs square wave-pulses.

2.3.2. Motor cortex mapping

A mapping procedure to locate the optimal stimulation site of motor cortex for eliciting MEP was performed using 70% of maximal stimulator output on the first training day. For the following examinations, 120% of RMT on the training day were used for mapping. A predefined pattern for coil movement was used for mapping during stimulations with 4 to 6 seconds randomised intervals. The stimulation location that evoked the highest regular peak-to-peak MEP amplitude in the right abductor pollicis brevis muscle was used for the TMS measurements. Abductor pollicis brevis was chosen as it provides high mapping reliability (Corneal et al., 2005). Left motor cortex was stimulated in all subjects as effects originating in left sensorimotor cortex (Mykland et al., 2018, Mykland et al., 2019) and other indications of asymmetric brain dysfunction in migraine (Schulte et al., 2020), have been previously reported. Interhemispheric differences of CSP duration, SICI and ICF between dominant and non-dominant hemispheres have mostly been reported to be minimal or absent (Säisänen et al., 2008, Menon et al., 2018).

2.3.3. Resting motor threshold

RMT was then determined using a standardised algorithm based on modified relative-frequency criterion (Groppa et al., 2012). Stimulation started at 35% maximal stimulator output, increasing stimulation intensity in steps of 5% maximal stimulator output until consistent MEPs above 50 μV was recorded. Then the intensity was lowered in steps of 1% maximal stimulator output until less than 5 out of 10 stimulations evoked MEPs above 50 μV. The lowest stimulation intensity evoking MEPs after at least 5 of 10 stimulations was used as RMT.

2.3.4. Cortical silent period

For CSP recording, the participants performed isometric abduction of the thumb against a Velcro band with instructions to use about 50% of maximum voluntary contraction (Fig. 2.A). Contraction force was assessed using predefined instructions for different levels of contraction to the participant during visual assessment of EMG activity. EMG was also visually evaluated during recording to ensure subject cooperation. The 50% maximum voluntary contraction have provided the most stable and informative CSP with little need for control in previous investigations (Säisänen et al., 2008). A TMS stimulation intensity of 120% RMT was used as this intensity has shown low variability for CSP duration in abductor pollicis bre-

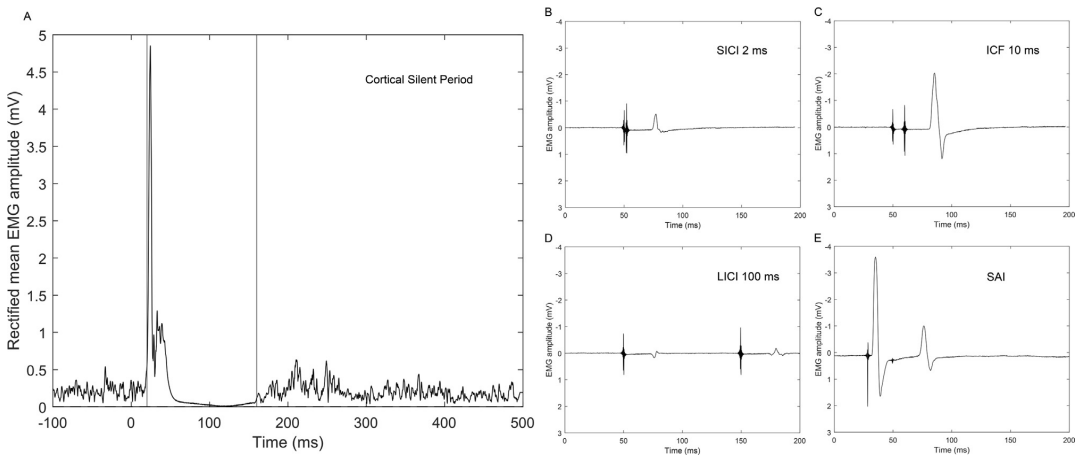

Fig. 2. Cortical silent period and paired pulse TMS illustrations. (**A**) Rectified mean electromyography (EMG) amplitude in millivolts (mV) during time in milliseconds (ms) for one session of Cortical silent period (CSP) recording for a single participant. EMG was recorded from the abductor pollicis brevis muscle in the right hand. Transcranial magnetic stimulation (TMS) was elicited at time 0 ms. Vertical solid lines indicate the CSP onset and offset. The increase in amplitude in the initial part of the CSP measurement is the motor evoked potential (MEP). (**B, C, D, E**) EMG amplitude (mV) from single recordings of paired pulse TMS (ppTMS); (**B**) Short-interval intracortical inhibition (SICI) with 2 seconds interstimulus interval (ISI), (**C**) Intracortical facilitation (ICF) with 10 seconds ISI, (**D**) Long-interval intracortical inhibition (LICI) with 100 seconds ISI and (**E**) Short-latency afferent inhibition (SAI) with 21 seconds ISI between median nerve stimulation and TMS. Each MEP is preceded by one or two transcranial magnetic stimulations for the different stimulation types and ISI or a median nerve stimulation and a transcranial magnetic stimulation for SAI, visible before the MEP as stimulus artefacts.

vis (Säisänen et al., 2008). Six measurements of CSP duration were gathered with 12 second intervals. Participants were instructed to maintain consistent force from 3 seconds before stimulation, until 2 seconds after stimulation.

2.3.5. Paired pulse transcranial magnetic stimulation

The ppTMS was performed as one continuous session in a predetermined block-randomised order equal for all subjects. We recorded responses to single stimulus of 120% RMT and five paired stimulation types: SICI with conditioning stimulus (CS) of 80% RMT and test stimulus (TS) of 120% RMT at interstimulus interval (ISI) 2 and 4 ms (Fig. 2B), ICF with CS of 80% RMT and TS of 120% RMT at ISI 8 and 10 ms (Fig. 2C) and LICI with CS of 109% RMT and TS of 120% RMT at ISI 100 ms (Fig. 2D). The different stimulation types were randomised for order in blocks of six. Twenty responses were recorded from the single test stimulus and from each paired stimulation type, amounting to a total of 120 responses recorded.

2.3.6. Short-latency afferent inhibition

SAI was recorded using electrical median nerve stimulation at the wrist as a conditioning stimulus with the cathode proximal (Fig. 2E) and 21 ms ISI (Tokimura et al., 2000, Turco et al., 2018). Median nerve motor threshold was determined as the lowest intensity eliciting a visible muscle twitch in the abductor pollicis brevis muscle. This intensity was then used for the conditioning stimulus. A TMS intensity of 120% RMT was used as TS. Alternating single TS and conditioned SAI were recorded with five seconds intervals until a total of 20 recordings were gathered for each of the two stimulation types.

2.4. Data analysis

Data were visually analysed for artefacts. LabChart version 8 was used to filter EMG (1 Hz – 2.5 kHz), to measure peak-to-peak amplitudes from blinded manual markings of each MEP and to rectify EMG for CSP duration measurements.

Custom made scripts in MATLAB R2019b (MathWorks, Natick, MA, USA) were used for averaging the rectified EMG from each trial and determining CSP duration for each subject. We used the mean consecutive difference threshold method (Hupfeld et al., 2020, Garvey et al., 2001) to automatically determine the offset of CSP. However, we defined MEP onset instead of offset as the onset of CSP to minimise error (Säisänen et al., 2008), and used an adaption of the threshold method to automatically define MEP onset. The upper threshold limit was calculated as 99.76% of the mean consecutive difference above the mean rectified EMG amplitude in the 100 ms pre-stimulus window. The first data point of the MEP above the upper limit was set as beginning of MEP (CSP onset) and the CSP offset was set at the first data point of the CSP above the lower limit where at least 50% of the next 5 ms of data points also were above the lower limit. Every onset and offset were visually inspected by an investigator blinded for diagnosis and sleep condition.

Breakthrough EMG was visually determined and included in the silent period as this activity is understood to be of spinal origin (Hupfeld et al., 2020, Zeugin and Ionta, 2021) or caused by increased muscle spindle firing from muscle relaxation (Škarabot et al., 2019). Thus, this activity was considered not relevant for the present evaluation of the cortical mechanisms of the silent period. However, we report the number of participants with breakthrough EMG as requested in current recommendations for future methodological considerations (Hupfeld et al., 2020). In the interictal migraine group, CSP from 22 examination days had breakthrough EMG in the silent period, distributed among 12 participants (25.5%). In the control group, CSP from 9 examination days had breakthrough EMG among 5 participants (17.2%).

Custom scripts in MATLAB R2019b (MathWorks, Natick, MA, USA) and STATA version 17.0 (StataCorp LP) were used to plot

figures which were then assembled in Adobe Photoshop CC 2019 (Adobe).

2.5. Statistical analysis

STATA version 17.0 (StataCorp LP) was used for statistical analyses. The outcome variable for CSP was the CSP duration in ms. Outcomes for ppTMS and SAI were peak-to-peak amplitude (mV) of each stimulation type. Linear mixed models (suited for handling missing data) were used for all analyses. Hence, migraineurs with at least one interictal recording were included in the models. Peak-to-peak amplitudes were transformed to the power of 0.2 to better meet model assumptions. Assumptions on residuals were investigated visually via histograms and q-q plots of residuals. The model used was determined as the model giving the lowest Akaike and Bayesian information criterion (AIC/BIC) between 2-level random intercept, random slope and random slope with unstructured covariances models, and a 3-level random intercept model. Results determined the use of a 2-level random intercept model for CSP duration with subject as level 2, and sleep, diagnosis and their interaction as fixed effects. For ppTMS, we used separate 3-level linear mixed random intercept models for each of the five paired stimulation types with test stimuli/stimulation type as level 2 and subject as highest level. Sleep, diagnosis, paired stimulation type and their interactions were included as fixed effects. Every ppTMS MEP amplitude was included in the model. The linear mixed models calculated degree of inhibitory/facilitatory effects from ppTMS variables as estimated marginal means.

A priori defined subgroups of interest for secondary analyses were MwoA/MA and NSM/SM. Migraineurs were categorised into subgroups according to answers from a questionnaire filled out the same day as the neurologist evaluation. MA was defined as migraine subjects having any percentage of attacks in form of or accompanied by aura symptoms. SM was defined as migraine subjects reporting attacks to usually start "upon awakening" or "during the night, awakening them from sleep". Migraineurs reporting attacks to usually start "during daytime before noon", "during daytime after noon" or at "no regular onset time" were classified as NSM.

Significant findings for primary and secondary objectives in Step 1 were further investigated in additional exploratory analyses (Step 2) for associations with each clinical variable in a separate model within the migraine group. Each of these models included the fixed effect of the variable, sleep condition and their interaction. The following clinical variables were evaluated: Attacks per month, usual attack duration, usual headache intensity, years since headache debut, usual attack allodynia, photophobia, phonophobia ("no" and "small" degree of symptoms merged due to low group sizes), osmophobia, and the common premonitory "dopaminergic" symptoms of yawning and mood change (Barbanti et al., 2020a). The "no-symptom" or "least-symptom" response categories were used as base in the models. Findings of primary analyses were further analysed with models where "measured sleep time" replaced the categorical SR-variable (Step 3) and models corrected for days since start of last menstruation cycle in eligible participants with cycles shorter than 36 days (Mihm et al., 2011) (Step 4), as the menstruation cycle may affect TMS measurements (Ziemann et al., 2015). Measured sleep time was extracted from actigraphy data, except for two examination days where actigraphy data was lacking and sleep diary was used.

Two-sided p-values < 0.05 are reported as significant and p-values < 0.10 are described as trends. We planned to recruit a larger migraine group permitting analyses of subgroups within migraine subjects and accounting for some migraine subjects to not have interictal recordings. Two-tailed Student's t-test on independent groups of sample size 30 and 45 with alpha 0.05 has 80% power to detect a medium to large Cohen's d effect size of approximately 0.67 (Cohen, 1988). We did not adjust for multiple comparisons as doing that would have assumed all null hypotheses to be true simultaneously and increased the likelihood of type II errors (Perneger, 1998).

3. Results

Clinical data, sleep time and demographic data are displayed in Table 1. Measured sleep time indicate similar sleep times for all groups with mean restricted sleep time between 4.1 and 4.4 h, constituting between 54% and 59% of habitual sleep. SR did not induce a significant difference on RMT between the main groups or subgroups.

3.1. Cortical silent period

Sleep restriction had an opposite effect on CSP duration in interictal migraine and controls, where the CSP duration was clearly reduced from 147.9 ms to 139.6 ms after restricted sleep in migraineurs (Fig. 3.A). Interaction effects on CSP duration are summarised in Table 2. We found a significant effect of the interaction interictal migraine vs controls × restricted sleep vs habitual sleep on CSP duration ($p = 0.046$) in the primary analysis. When replacing sleep condition with measured sleep time in minutes in the model, the effect of the corresponding interaction was still significant ($p = 0.038$). The diagnose × sleep condition interaction was also significant when controlling for days since start of last menstruation as a covariate ($p = 0.018$). Post hoc effects of sleep condition on CSP duration in the separate groups revealed a trend for lower CSP duration after SR in interictal migraineurs ($p = 0.076$, *95% CI* −17.5 to 0.9), and no significant effect of SR for controls ($p = 0.31$, *95% CI* −4.0 to 12.7). Post hoc contrast effect of diagnosis on CSP duration for each sleep condition separately was not significant for either habitual sleep ($p = 0.28$, *95% CI* −8.6 to 29.7) or restricted sleep ($p = 0.83$, *95% CI* −21.4 to 17.2).

Similar patterns to the SR induced decrease in CSP duration for interictal migraine also appeared for both the MA and MwoA group separately, although more pronounced for MA (Fig. 3.B). We analysed the subgroups MwoA, MA and CO in one linear mixed model (Table 2). The effect of the interaction MA/CO × sleep condition on CSP duration was significant ($p = 0.017$). The interactions MwoA/CO × sleep condition ($p = 0.33$) and MA/MwoA × sleep condition ($p = 0.20$) was not significant. Post hoc contrasts revealed a significant effect of sleep restriction on CSP duration in MA ($p = 0.030$, *95% CI* −28.58 to −1.43).

NSM did also display a pattern of decreased CSP duration after SR as in interictal migraine, while SM resembled the pattern of controls (Fig. 3.C). When statistically evaluating the migraine subgroups SM, NSM and CO in the same model (Table 2), we observed a significant interaction effect with sleep condition on CSP duration for NSM/CO ($p = 0.002$) and SM/NSM ($p = 0.007$), while the interaction for SM/CO was not significant ($p = 0.68$). Post hoc contrasts revealed a significant effect of sleep condition on CSP duration in the NSM group ($p = 0.002$, *95% CI* −27.83 to −6.15).

More severe clinical symptoms were associated with shorter CSP duration for several variables. SR decreased CSP duration more in interictal migraineurs with frequent attacks, greater degree of photophobia, phonophobia and osmophobia, and premonitory yawning (Fig. 3.D-I). For both sleep conditions combined, we observed shorter CSP duration for interictal migraineurs with higher allodynia score and greater degree of photophobia, phonophobia osmophobia, premonitory yawning and premonitory mood changes (Fig. 3.D-I). No effects were found for usual attack duration, usual attack intensity or years with headache. We found these

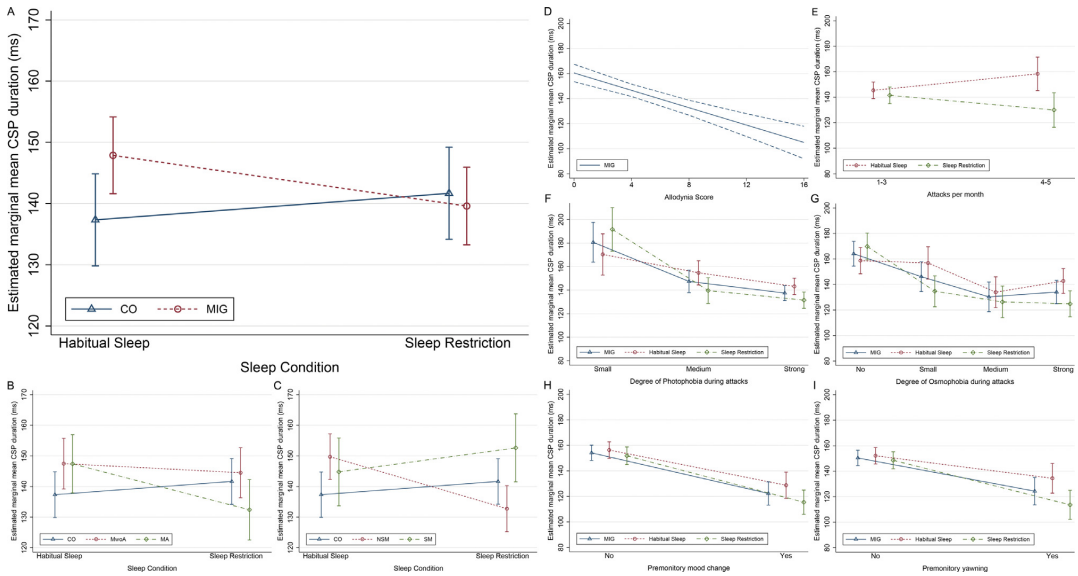

Fig. 3. Estimated marginal means of cortical silent period (CSP) duration. (**A, B, C**) Estimated marginal means of cortical silent period (CSP) duration in milliseconds (ms) from random intercept models of interaction with diagnosis and sleep condition in interictal migraine and controls. (**A**) Blue line and triangles represent healthy controls (CO), and red line and circles represent interictal migraineurs (MIG). We found a significant interaction effect of MIG/CO × sleep restriction/habitual sleep (p = 0.046), where MIG displayed reduced CSP duration after sleep restriction. (**B, C**) The corresponding interaction effect was more pronounced for the non-sleep related migraine (NSM) (p = 0.002) and migraine with aura (MA) (p = 0.017) groups compared to controls. In **(B)** red lines and circles represent migraine without aura (MwoA), and green lines and diamonds represent MA. In **(C)** red lines and circles represent NSM, and green lines and diamonds represent sleep related migraine (SM). (**D-I**) Clinical variables with significant effects on CSP duration in linear mixed models which included the clinical variable, sleep condition and their interaction. (**D-I**) Blue lines represent the main effect of the clinical variable on CSP duration in the model. Red and green lines show the effect separated for sleep conditions. **(A-I)** Capped spikes represent estimated marginal standard error. All migraine subjects were interictal with a 24-h cut off from the ictal phase.

Table 2
The effects of sleep restriction on cortical silent period (CSP) duration in interictal migraine compared to controls.

Models for interaction effects on CSP duration	**n**	**z**	**p**	**95% CI**	
MIG/CO × restricted/habitual sleep	46/29	−2.00	**0.046***	−25.0	−0.3
MIG/CO × sleep time[a]	46/29	2.07	**0.038***	0.004	0.12
MIG/CO × restricted/habitual sleep controlled for menstrual cycle[b]	27/14	−2.36	**0.018***	−47.4	−4.4
MwoA/MA/CO	27/19/29				
MwoA/CO × restricted/habitual sleep		−0.97	0.33	−22.0	7.4
MA/CO × restricted/habitual sleep		−2.39	**0.017***	−35.2	−3.5
MA/MwoA × restricted/habitual sleep		−1.29	0.20	−30.3	6.2
NSM/SM/CO	32/14/29				
NSM/CO × restricted/habitual sleep		−3.12	**0.002***	−34.7	−7.9
SM/CO × restricted/habitual sleep		0.41	0.68	−13.1	20.1
SM/NSM × restricted/habitual sleep		2.68	**0.007***	6.6	43.0

The table displays results from 2-level random intercept models, including number of subjects (n), test statistic assuming normal distribution (z), p-value (p) and 95% confidence intervals (CI) for cortical silent period (CSP) in milliseconds (ms). MIG = Interictal migraine; CO = Healthy controls; MwoA = Migraine without aura; MA = Migraine with aura; NSM = Non-sleep related migraine; SM = Sleep related migraine.
* and **bold** indicate $p < 0.05$.
[a] CI for the effect per minute of restricted sleep.
[b] This model does only include female migraineurs, controlling for the effect of days since start of last menstruation. Excluded examination days > 35 days from start of menstruation (n = 6 examinations, range 41–90 days).

associations as a significant interaction effect on CSP duration between sleep condition and attacks per month category 3 vs 2 (p = 0.033, *95% CI* −46.9 to −1.9; all subjects were in those 2 categories), strong and medium vs small degree of photophobia (p = 0.015, *95% CI* −59.4 to −6.5; p = 0.017, *95% CI* −66.4 to −6.5) and strong and small degree vs no osmophobia (p = 0.008, *95% CI* −50.3 to −7.7; p = 0.003, *95% CI* −55.1 to −11.5). Additionally, we found a trend for medium vs no osmophobia (p = 0.079, *95% CI* −39.5 to 2.2), strong vs small phonophobia (p = 0.065, *95% CI* −42.6 to 1.3) and premonitory yawning (p = 0.084, *95% CI* −36.8 to 2.4). We also found significant main contrast effects on CSP duration regardless of sleep in the same model for allodynia score (ASC-12) (p = 0.001, *95% CI* −5.6 to −1.4), strong vs small degree of photophobia (p = 0.017, *95% CI* −78.7 to −7.7), strong and medium vs small phonophobia (p = 0.005, *95% CI* −64.6 to −11.3; p = 0.023, *95% CI* −58.2 to −4.2), strong and medium vs no osmophobia (p = 0.024, *95% CI* −56.1 to −3.9; p = 0.025, *95% CI* −63.5 to −4.2), premonitory yawning (p = 0.034, *95% CI* −50.2 to −2.0)

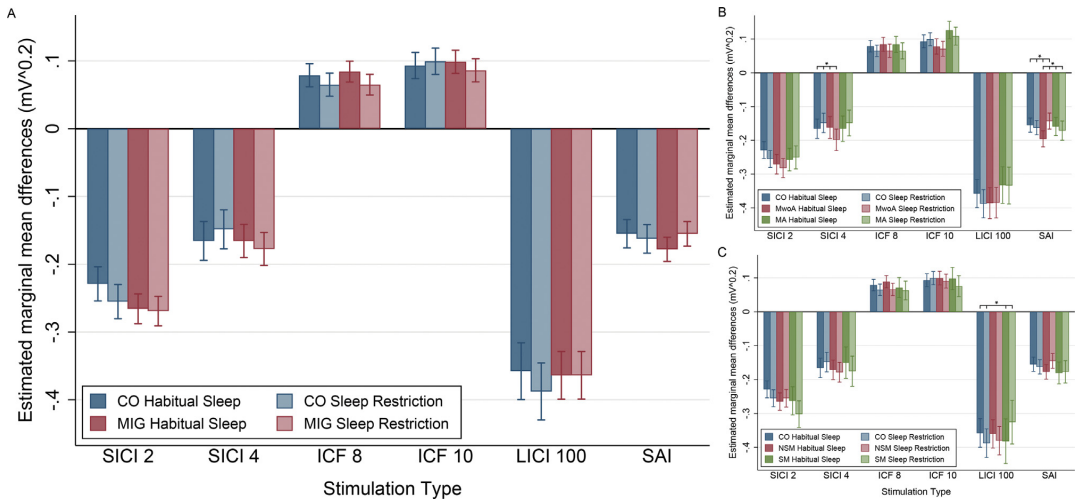

Fig. 4. Estimated marginal means of paired pulse transcranial magnetic stimulation (ppTMS) and short-latency afferent inhibition. Figures display estimated marginal mean motor evoked potential (MEP) amplitude differences in millivolts to the power of 0.2 ($mV^{0.2}$) between each paired pulse type and test stimuli for different groups and sleep conditions. Models were separate random intercept models for each stimulation type including groups, sleep condition and each stimulus type. Capped spikes represent estimated marginal standard error. All migraine subjects were interictal with a 24-h cut off from the ictal phase. X-axis numbering indicate interstimulus interval (ISI) for each stimulus type in milliseconds (ms). (**A**) We found no significant interaction effects for the groups interictal migraine (MIG)/healthy controls (CO). (**B**) Secondary subgroup analyses revealed significant interaction effects of group, sleep condition and stimulation type for short-interval intracortical inhibition (SICI) 4 ms in migraine without aura (MwoA)/CO and short-latency afferent inhibition (SAI) in MwoA/CO and MwoA/migraine with aura (MA). (**C**) Secondary subgroup analyses revealed a significant interaction effect of group, sleep condition and stimulation type for long-interval intracortical inhibition (LICI) 100 ms in sleep related migraine (SM)/CO. No significant interaction effects were found for intracortical facilitation (ICF). * Indicate interaction effects with p-value < 0.05.

Table 3
The effects of restricted sleep on intracortical inhibition and facilitation in interictal migraine and controls, as measured by paired pulse TMS induced motor evoked potentials.

Models for interaction effects on MEP amplitude	n	z	p	95% CI	
MIG/CO × restricted/habitual sleep × paired stimulation type/test stimulation	44/29				
SICI 2 ms		0.98	0.33	−0.02	0.07
SICI 4 ms		−1.30	0.20	−0.07	0.01
ICF 8 ms		−0.25	0.80	−0.05	0.04
ICF 10 ms		−0.90	0.37	−0.06	0.02
LICI 100 ms		1.23	0.22	−0.02	0.08

The table displays results from 3-level random intercept models, including number of subjects (n), test statistic assuming normal distribution (z), p-value (p) and 95% confidence intervals (CI) for change of motor evoked potential (MEP) amplitude in millivolt (mV) transformed to the power of 0.2. MIG = Interictal migraine, CO = Healthy controls; TMS = Transcranial magnetic stimulation; SICI = Short-interval intracortical inhibition; ICF = Intracortical facilitation; LICI = Long-interval intracortical inhibition. Each paired-pulse stimulation type measurement is displayed with the corresponding interstimulus interval.

and premonitory mood changes (p = 0.004, *95% CI* −53.3 to −10.4). In addition, we found a trend for medium vs small degree of photophobia (p = 0.087, *95% CI* −71.4 to 4.8).

3.2. Paired pulse transcranial magnetic stimulation

We did not observe any pattern of differences in the effect of SR on ppTMS variables between interictal migraine and controls (Fig. 4.A). Interaction effects of SR and diagnosis on ppTMS are presented in Table 3 and Supplementary Table 1. SICI was increased after SR in MwoA compared to controls, but only for 4 ms ISI (Fig. 4.B). LICI was decreased in SM after SR compared to controls (Fig. 4.C). The effect of SR on SICI for MwoA was seen as a significant interaction effect vs controls of sleep condition and SICI 4 ms (p = 0.0498), while SR had a significant interaction effect on LICI 100 ms for SM subjects compared to controls (p = 0.030) and a trend for SM compared to NSM (p = 0.073). The remaining interaction effects of SR and diagnosis on ppTMS and post hoc contrasts between interictal migraine and controls for habitual sleep were non-significant. Post hoc analysis showed that the effect of SR on SICI 4 ms was not significant for the MwoA group (p = 0.12, *95% CI* −0.08 to 0.009). The same post hoc contrast for the effect of SR on LICI did not reach significance in SM subjects (p = 0.12, *95% CI* −0.02 to 0.13).

3.3. Short-latency afferent inhibition

The effect of SR on SAI did not differ between interictal migraine and controls, but we detected a decrease in SAI after SR for MwoA compared to controls and MA (Table 4, Fig. 4.B). The interactions group × sleep condition × stimulation type was significant for both MwoA/CO (p = 0.023) and MA/MwoA (p = 0.045). Post hoc interaction sleep condition × stimulation type was significant for MwoA alone (p = 0.016, *95% CI* 0.01 to 0.10), indicating that SR was able to reduce this inhibitory effect among MwoA subjects. SAI did not differ between interictal migraine subjects and controls after habitual sleep.

Table 4
The effects of sleep restriction on Short-latency Afferent Inhibition (SAI) in interictal migraine compared to controls.

Models for interaction effects on MEP amplitude	n	z	p	95% CI	
MIG/CO × restricted/habitual sleep × paired stimulation type/test stimulation	46/29	1.38	0.17	−0.01	0.07
MwoA/MA/CO × restricted/habitual sleep × paired stimulation type/test stimulation	27/19/29				
MwoA/CO		2.28	**0.023***	0.008	0.11
MA/CO		−0.16	0.87	−0.06	0.05
MA/MwoA		−2.01	**0.045***	−0.13	−0.002
NSM/SM/CO × restricted/habitual sleep × paired stimulation type/test stimulation	32/14/29				
NSM/CO		1.61	0.11	−0.009	0.09
SM/CO		0.34	0.74	−0.05	0.07
NSM/SM		−0.84	0.40	−0.10	0.04

The table displays results from 3-level random intercept models, including number of subjects (n), test statistic assuming normal distribution (z), p-value (p) and 95% confidence intervals (CI) for change of motor evoked potential (MEP) amplitude in millivolt (mV) transformed to the power of 0.2. All effects are for interactions of two groups × restricted/habitual sleep × stimulation type. MIG = Interictal migraine; CO = Healthy controls; MwoA = Migraine without aura; MA = Migraine with aura; NSM = Non-sleep related migraine; SM = Sleep related migraine.
* and **bold** indicate $p < 0.05$.

4. Discussion

4.1. Main findings

The most important finding in the present study was a significant decrease in CSP duration after SR in interictal migraine compared to controls. This finding was more pronounced for MA and the NSM subgroup, where the latter consisted of migraine subjects usually not having attacks during or at the end of sleep. Decreased CSP duration after SR was also associated with greater number of attacks per month, increased ictal photophobia, phonophobia and osmophobia, and premonitory yawning. Furthermore, generally shorter CSP duration was associated with increased ictal symptoms of hypersensitivity in the form of allodynia, photophobia, phonophobia and osmophobia, and premonitory yawning and mood change. On the other hand, we did not detect consistent effects of sleep restriction on ppTMS or SAI measures, neither for intracortical facilitation nor inhibition. However, in secondary analyses SICI 4 ms was more increased and SAI more decreased after SR in MwoA, while LICI was more reduced after SR in SM. Our present findings may suggest that SR modifies some, but not all, inhibitory GABAergic systems in migraine. The effect seems to differ between migraine subgroups. The cause and mechanisms are still unknown, but a dysregulation of dopaminergic pathways interictally among migraine subjects could be a possible explanation.

4.2. CSP in interictal migraine

Although sleep related changes of CSP to our knowledge has not been investigated in migraine, several authors have reported on migraine-control differences. Five previous studies did not report any significant difference between the CSP duration of interictal migraine and controls (Áfra et al., 1998, Werhahn et al., 2000, Siniatchkin et al., 2007, Siniatchkin et al., 2009, Gunaydin et al., 2006). Likewise, we did not detect any significant difference in CSP duration between migraineurs and controls after habitual sleep in this study. However, shorter CSP duration has been reported for interictal migraine (Khedr et al., 2006), in the subgroups of MA (Maier et al., 2011, Aurora et al., 1999), female migraineurs (Neverdahl et al., 2017) and preovulatory recordings (Yuksel and Topalkara, 2021), and specifically for facial CSP duration (Curra et al., 2007). In summary, there is no consistent evidence of altered CSP duration after habitual sleep in the migraine group as a whole. However, some limited evidence may suggest that reduced CSP duration is a potential biological marker for certain migraine subgroups.

4.3. CSP and GABAergic activity

Reduced CSP duration after SR in interictal migraine can be interpreted as reduced cortical inhibitory effect on motor cortex output mediated by GABA-B receptors (Ziemann et al., 2015, Hupfeld et al., 2020). However, the mechanisms of CSP are complex and are not yet fully understood. The inhibitory effect early in the CSP is partly constituted by spinal mechanisms and is increased by GABA-A receptor mediated activity. Later in long CSPs (>200 ms) the inhibitory effect is decreased by GABA-A receptor activity (Ziemann et al., 2015, Hupfeld et al., 2020). Consequently, it is not known whether the alterations we observed was mainly mediated by GABA-A or GABA-B receptors. Nevertheless, an impaired GABAergic inhibition after SR, which our findings are in line with, support some previous indications of reduced cortical inhibition in migraine (Brighina et al., 2009b). Impaired thalamocortical drive has been suggested to explain such a dysfunctional cortical inhibition in migraine (Magis et al., 2016). If we interpret our results in this pathophysiological model, SR may alter an impaired thalamocortical system differently in migraine, and consequently affect cortical inhibition abnormally.

CSP duration and LICI have previously been observed to progressively decrease throughout the day. This link between circadian rhythm and GABAergic inhibition may be related to corticotropin-releasing hormone from the paraventricular nucleus of hypothalamus (Lang et al., 2011). Thus, altered hypothalamic function in the interictal phase of migraine (Moulton et al., 2014) may be related to reduced CSP duration after sleep restriction in migraineurs by suppressing corticotropin-releasing hormone release. However, we did not observe concurrent effects on LICI which is contradictory to this hypothesis. Time of day during recording is not described in studies that reported reduced CSP duration in interictal migraine (Curra et al., 2007, Khedr et al., 2006). Consequently, later recording of CSP duration in migraineurs may be another possible explanation for the previously observed reduced CSP duration which we did not find after habitual sleep in this study.

4.4. CSP and the dopaminergic system

Premonitory symptoms of yawning and mood change, and osmophobia, are thought to reflect dopaminergic neurotransmission (Guven et al., 2018). These symptoms were associated with generally shorter CSP durations in this study. In addition, yawning and osmophobia were associated with shortened CSP duration after SR. Dopaminergic mechanisms is known to increase the inhibitory CSP effect as shown by studies of the dopamine receptor D1/D2 agonist pergolide mesylate (Ziemann et al., 1996) and levodopa

(Priori et al., 1994). Both cortical and subcortical areas are likely to be involved in the CSP inhibitory effect (Zeugin and Ionta, 2021, Ziemann et al., 2015). Furthermore, yawning is seemingly elicited by dopamine D2 receptor activation, and inhibited by dopamine receptor D1 activation and by increased levels of circulating estrogens (Sanna et al., 2012, Argiolas and Melis, 1998). Estrogen-drops are well known to induce migraine attacks (Chai et al., 2014), implying a possible association with dopaminergic dysregulation in migraine. Premonitory yawning has also been shown to be associated with allodynia in migraine (Guven et al., 2018, Barbanti et al., 2020a), and allodynia had a similar and strong effect on CSP duration in our dataset.

After sleep deprivation of healthy subjects, dopamine receptors are thought to be downregulated in striatum (Volkow et al., 2012) while thalamic activity increases (Tomasi et al., 2009), possibly to compensate for reduced dopaminergic signalling which worsens signal to noise efficiency of neuronal activation (Tomasi et al., 2016). Dopaminergic cells in ventral periaqueductal gray matter have an ascending waking effect with projections to thalamus and other wake-sleep regulators (Lu et al., 2006). Additionally, the ventral periaqueductal gray is also known to play a role in pain regulation (Li et al., 2016). Although speculative, it is possible that an abnormal dopaminergic system in migraine (Barbanti et al., 2013, Schulte et al., 2020) has an altered response to lack of sleep. Possible consequences may be altered thalamic compensation or a direct dopaminergic effect on GABAergic neurons (Floran et al., 1997, Beauregard and Ferron, 1991). In the interictal phase when most migraineurs typically do not experience symptoms, these small alterations may be compensated for. However, the association between CSP duration and ictal symptoms in this study indicate that this underlying vulnerability may play a role in the mechanisms of attacks.

Supporting this pathophysiological model of an abnormal dopaminergic system in migraine, altered dopamine D2/D3 receptor availability in striatum has been found during headache and ictal allodynia in migraine (DaSilva et al., 2017). Furthermore, dopaminergic hypofunction and dopamine receptor dysregulation has also previously been reported in migraine (Barbanti et al., 2013). Thus, it is interesting to note that dopamine modulates thalamocortical information integration (Lavin and Grace, 1998) and that dopamine D1 receptors in ventrobasal thalamus mediate postsynaptic membrane depolarisation, possibly by suppression of ATP-sensitive inward-rectified K + channels (Govindaiah et al., 2010). These channels have recently been strongly implied in migraine pathophysiology (Al-Karagholi et al., 2017).

4.5. Intracortical facilitation and inhibition

Our analyses of ppTMS and SAI in interictal migraine and controls, did not show any significant interactions with sleep or differences between the groups for habitual sleep. Effects of sleep restriction on ppTMS and SAI has, to our knowledge, not been investigated in migraine before. However, our data on habitual sleep are consistent with most previous studies in interictal migraine (Siniatchkin et al., 2007, Conforto et al., 2012, Cosentino et al., 2018, Neverdahl et al., 2017, Werhahn et al., 2000), except for two reports of increased ICF (Siniatchkin et al., 2007, Cosentino et al., 2018) and one of decreased SICI (Neverdahl et al., 2017). On the other hand, we found some effects of SR on ppTMS and SAI for subgroups of migraine. Understanding the mechanisms behind ppTMS and SAI may also enhance our understanding of the effects observed on CSP duration. Both SICI and LICI seemingly reflects GABAergic inhibitory mechanisms. The inhibitory SICI-effect represent post synaptic inhibition mediated via α2 and α3 subunits of GABA-A receptors, being controlled by presynaptic GABA-B mediated autoinhibition (Ziemann et al., 2015, Florian et al., 2008). LICI is thought to represent GABA-B receptor mediated inhibitory post-synaptic potentials (ISPS) (McDonnell et al., 2006). Although not yet fully understood, this GABA-B mediated effect is probably partly different from that of CSP (Tremblay et al., 2013). LICI may reflect magnitude of inhibition to a greater degree, whereas CSP also represent some temporal aspects (Paci et al., 2021). CSP is also more dependent on the dose of GABAergic drugs, while LICI is saturated at lower levels of GABA; Suggesting different effects on these measurements from different relative levels of GABA available in the synaptic cleft (Benwell et al., 2007). Thus, if GABAergic inhibition is slightly reduced interictally in migraine, sleep restriction may enhance this effect to a level where CSP duration is reduced without reaching the levels where the LICI effect is no longer saturated.

4.6. Migraine with and without aura

Our secondary analyses suggest that MA and MwoA subgroups are different with respect to their interictal excitation/inhibition balance. SR-induced CSP duration decrease was clearly most pronounced in the MA subgroup. On the other hand, SICI (4 ms ISI) and SAI were slightly altered by SR in MwoA, although no definite consistent pattern emerged from paired pulse responses in our study. One previous study have indicated reduced SAI between attacks in migraine, interpreted from a greater MEP amplitude slope between different ISI (Coppola et al., 2020), while another study of SAI reported no interictal difference to controls (Alaydin et al., 2019). SAI is suggested to be mediated via α1 subunits of GABA-A receptors and affected by cholinergic projections from paramedian thalamic nuclei to primary motor cortex and recruitment of primary motor cortex inhibitory interneurons by projections from primary somatosensory cortex (Turco et al., 2018). SICI is also probably under cholinergic modulation (Ziemann et al., 2015). A SR-induced imbalance related to the function of different subunits of GABA-A receptors or cholinergic projections could be hypothesised in MwoA, but no definite pattern emerged for the full excitatory-inhibitory analyses.

4.7. Sleep and non-sleep related migraine

The significant decrease in CSP duration after sleep restriction in interictal migraine was more pronounced for the NSM subgroup, while the effect in the SM subgroup seemed similar to the effect in the control group. Results from previous investigations of polysomnography and subjective sleep evaluation in NSM has been interpreted as NSM having reduced arousability or being relatively sleep deprived, with accompanying lowered pain thresholds before the polysomnography measurements (Engstrøm et al., 2014). A recent study from our group also discovered that this increased pain sensitivity in NSM did not increase further after SR, while such an increase was seen as a trend among SM (Neverdahl et al., 2021). These findings suggest the duration of CSP as measured here, not to be directly associated with current pain thresholds. However, because symptoms attributed to the dopaminergic system were associated with decreased CSP duration in the present study, it may be hypothesised that dopaminergic dysfunction is more pronounced in NSM than SM subjects. It is known that dopamine D1-like and dopamine D2-like receptors in hypothalamus and periaqueductal gray exert different and sometimes opposite effects on nociception where dopamine D2-like receptors often are antinociceptive (Tobaldini et al., 2018, Li et al., 2019). Thus, a dopamine receptor dysfunction and/or imbalance may be related to baseline altered pain thresholds in NSM with normal CSP duration. Furthermore, possible dopaminergic alteration induced by SR may affect the dopamine receptor balance in a different way or location, causing reduced CSP duration without further altering pain thresh-

olds. Interestingly, polymorphisms in dopamine receptor genes have also been implied in migraine (Akerman and Goadsby, 2007). However, whether such mechanisms are relevant for the pathophysiology of NSM are still speculative.

4.8. Strengths and limitations

We performed a randomised, blinded and matched crossover study. Blinding is crucial for neurophysiological studies in migraine (Sand, 2014). We encourage future studies to apply such methods.

We included a larger migraine group to allow for a limited amount of predefined subgroup analyses. However, these subgroup analyses have lower power and should be interpreted accordingly. We did not correct for multiple analyses as that would have assumed all null hypotheses to be true simultaneously (Perneger, 1998).

We applied a feasible and known method of SR in this study. However, other study designs might enhance effect sizes. Complete sleep deprivation, rapid eye movement (REM)-sleep deprivation or sleep fragmentation could have induced different effects.

We used a 24-h cut off for the interictal phase in this study. However, some previous findings suggest the preictal phase to possibly last up to 48 h before the headache attack (Peng and May, 2020). Some early preictal and late postictal properties might theoretically have been included in the effects. However, this small theoretical overlap would only apply for a minor portion of our subjects and the exact length of the preictal or postictal phase for each subject is currently unknown.

We prohibited caffeine consumption on the day of testing as acute caffeine intake may have effects on CSP or ICF (Turco et al., 2020). Thus, there is a possibility that participants with high daily caffeine consumption may have been subject to caffeine withdrawal during examinations as a confounding factor with unknown effects on cortical excitability.

We utilised biphasic waveforms in contrast to the conventional monophasic posteroanterior current used for similar TMS investigations. We made this choice to follow up on a previous study we performed using biphasic stimulation waveforms in migraine (Neverdahl et al., 2017). The different current direction and waveforms are also largely comparable, at least for SICI and ICF responses (Wessel et al., 2019). However, there is a possibility that findings in previous pharmacologic TMS-studies with monophasic waveforms do not directly apply to biphasic stimulation responses.

We allowed for people with infrequent tension-type headache as controls, in accord with our practice from multiple headache studies for several decades in our university hospital. However, we excluded people with painful headache either having that headache one day per month or more, having consulted a doctor about the headache or who usually used medications for that headache. Control subjects were interviewed by an experienced headache nurse. It is accordingly unlikely that people with undiagnosed, infrequent primary headache have been included as healthy controls.

One previous study of SAI in migraineurs utilised a predefined ISI of 21 ms as in this study (Alaydin et al., 2019), while another applied ISI relative to individual N20 measurements (Coppola et al., 2020). Whether such adjustments provide increased precision have been uncertain (Turco et al., 2018). However, because more recent findings have revealed similar reliability between the two approaches (Turco et al., 2021), this is unlikely to represent a significant limitation in our design.

4.9. Conclusion

We found reduced CSP duration after sleep restriction in migraineurs during the interictal period compared to controls. This effect is likely mediated by reduced inhibitory GABA-B activity, and possibly modulated by both GABA-A activity and dopaminergic mechanisms related to wakefulness. In subgroup analyses, reduced CSP duration was demonstrated for migraine with aura and for migraineurs with non-sleep related attacks. GABAergic mediated CSP inhibition correlated with increased premonitory "dopaminergic" symptoms and ictal symptoms of hypersensitivity. However, migraine subjects without aura displayed a different pattern of results, and secondary analyses suggested slightly altered GABA-A mediated inhibition after sleep restriction. Finally, uncontrolled sleep deprivation status during examinations or a different composition of migraineurs with sleep related or non-sleep related attacks may account for a part of the inconsistencies between previous studies of migraine pathophysiology. Further investigations into distinct mechanisms between these subgroups may reveal implications of differentiated GABA or dopamine targeted treatment.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The authors report no conflicts of interest relevant to the manuscript. T.W.M. received speaker honoraria from Roche in 2018. E.T. has received personal fees for lectures and advisory boards from Lundbeck, Allergan/Abbvie, Roche, TEVA, Novartis, Amgen, Eli-Lilly. He is board member and shareholder of Palion Medical AS and shareholder of Nordic Brain Tech AS (NTNU spin-off companies). D.W.D. have provided consulting for Amgen, Atria, Cerecin, Cooltech, Ctrl M, Allergan, Biohaven, GSK, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Genentech, Nocira, Perfood, Praxis, AYYA Biosciences, Revance; Received honoraria from Vector psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix Communications, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press; Provided Research Support for Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI); Is involved with/as Stock Options/Share holder/Patents/Board of Directors of Ctrl M (options), Aural analytics (options), ExSano (options), Palion (options), Healint (Options), Theranica (Options), Second Opinion/Mobile Health (Options), Epien (Options/Board), Nocira (options), Matterhorn (Shares/Board), Ontologics (Shares/Board), King-Devick Technologies (Options/Board), Precon Health (Options/Board), AYYA Biosciences (Options), Atria Health. Patent 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis.

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Disclosure

All authors have approved the final version of the manuscript. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Data availability

Raw data were generated at the Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology. Derived data supporting the findings of this study may be available from the corresponding author on request.

Appendix A. Supplementary material

Supplementary tables of subgroup statistical analyses for paired pulse TMS. Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2022.04.004.

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Insufficient sleep may alter cortical excitability near the migraine attack: A blinded TMS crossover study

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Abstract

Background: Migraine is a brain disorder with a multifaceted and unexplained association to sleep. Brain excitability likely changes periodically throughout the migraine cycle. In this study we examine the effect of insufficient sleep on neuronal excitability during the course of the migraine cycle.

Methods: We examined 54 migraine patients after two nights of eight-hour habitual sleep and two nights of four-hour restricted sleep in a randomised, blinded crossover study. We performed transcranial magnetic stimulation and measured cortical silent period, short- and long-interval intracortical inhibition, intracortical facilitation and short-latency afferent inhibition. We analysed how responses changed before and after attacks with linear mixed models.

Results: Short- interval intracortical inhibition was more reduced after sleep restriction compared to habitual sleep the shorter the time that had elapsed since the attack ($p = 0.041$), and specifically in the postictal phase ($p = 0.013$). Long-interval intracortical inhibition was more increased after sleep restriction with time closer before the attack ($p = 0.006$), and specifically in the preictal phase ($p = 0.034$). Short-latency afferent inhibition was more decreased after sleep restriction with time closer to the start of the attack ($p = 0.026$).

Conclusion: Insufficient sleep in the period leading up to a migraine attack may cause dysfunction in cortical GABAergic inhibition. The results also suggest that migraine patients may have increased need for sufficient sleep during a migraine attack to maintain normal neurological function after the attack.

Keywords

TMS, GABA, cholinergic, preictal, postictal, hypothalamus

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Introduction

The connection between migraine and sleep has been well known for 150 years (1) but is still largely unexplained. However, brain regions such as the hypothalamus appear to be involved in both sleep physiology and migraine pathophysiology, possibly producing premonitory symptoms such as yawning and sleep disturbances (2,3). Sleep is also commonly used to end the migraine attack (4), but a large portion of migraine patients still experience postdromal symptoms such as fatigue after waking up (5). Furthermore, sleep

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disturbances are commonly known to trigger migraine attacks (6). These observations imply a close relationship between sleep physiology and migraine pathophysiology, signifying a potential to discover migraine specific mechanisms by manipulating sleep.

Migraine is suggested to be a cycling disease, possibly driven by periodic changes in the neuronal excitability of the hypothalamo-thalamo-brainstem network. This central nervous dysfunction may be represented by gradual decrease of sensory threshold towards an attack before gradual recovery after attacks (7). The preictal phase just prior to the onset of migraine headache encompass connectivity changes involving dopaminergic centres (8) and the hypothalamus (9). The preictal phase may also be characterised by increased somatosensory excitability in the brainstem and cortex, possibly caused by decreased intracortical inhibition (10). Preictal patterns in electroencephalography (EEG) may be indicative of underlying thalamocortical dysrhythmia (11), able to cause increased cortical synchronicity (12,13), which has been interpreted as reduced cortical preactivation (14). In the ictal phase, the increased somatosensory excitability (10,14), connectivity changes (9,15), and the reduced cortical preactivation before the attack (11,14) may flip or normalise towards interictal levels. Less is known about the postictal phase (16), but one group have found slight alterations of postictal brainstem functionality (17). Another group found an inverse relation between lateral inhibition and days elapsed since the last migraine attack (18). More detailed central nervous system (CNS)-excitability mapping with other methods is needed to understand the neurological changes leading up to the attack and accompanying the gradual symptomatic normalisation after the attack.

Sleep restriction as an experimental model of insufficient sleep has previously been shown to affect cortical responses in healthy volunteers (19) and we have recently shown that sleep restriction alters GABAergic inhibition in interictal migraine patients compared to controls (20). Thus, sleep restriction may amplify differences in neurological functioning which are usually subtle or compensated, allowing us to measure dynamics of migraine mechanisms which are specific to parts of the migraine cycle and reactive to sleep changes.

Several aspects of cortical excitability can be studied with transcranial magnetic stimulation (TMS). TMS-measurements of interest include the cortical silent period (CSP), paired pulse TMS (ppTMS) techniques as short- and long-interval intracortical inhibition (SICI and LICI) and intracortical facilitation (ICF), and short-latency afferent inhibition (SAI). These responses represent different facilitatory and inhibitory mechanisms (21). Thus, combining these responses allows for detailed investigation of cortical excitability and the actual mechanisms behind it.

We hypothesised that changes in sleep duration affect cortical functioning differently throughout the time leading up to an attack and during the time following an attack, and that the effects will be most pronounced in the preictal and postictal phases of the migraine cycle. We measured effects of excitatory and inhibitory systems after both habitual sleep and sleep restriction by recording responses to different TMS protocols. The primary objective was to evaluate how the effect of restricted sleep on TMS-measurements of cortical excitability vary with time from the end of the previous and time to the start of the next migraine headache attack. A secondary objective was to estimate how the effects of restricted sleep on TMS-measures varied with preictal, ictal and postictal states, as compared to the interictal state. We also performed exploratory evaluations of how sleep related effects of TMS varied with clinical migraine characteristics.

Methods

Subjects

Migraine subjects were recruited through media and social media and screened by headache nurses. Migraine subjects considered eligible were further evaluated by a neurologist for inclusion, requiring a diagnosis of migraine with or without aura according to The International Classification of Headache Disorders, 3rd edition (22) and meeting predefined criteria. We included migraine subjects between 18 and 65 years of age having between one and six attacks per month during the last six months. Prophylactic treatment for migraine was not permitted from four weeks before the first examination and throughout the whole examination period. Migraine patients were excluded if they had tension type headache for seven days or more per month. Exclusion criteria also included known sleep disorders, metabolic, endocrine or neuromuscular disorders, connective tissue disorder, neoplastic disease, cerebrovascular disease, symptomatic heart disease, lung disease or neurological/psychiatric disease with reduced function, treated hypertension or blood pressure >160/110 mmHg, acute infectious or painful disease, acute injury, previous craniotomy, pregnancy, alcohol or narcotics abuse, regular treatment with neuroleptics, antiepileptic drugs, antidepressants or other medications affecting neural, vascular or muscular function and contraindications for TMS. Subjects were asked not to exercise or to consume caffeinated beverages or tobacco on the examination days. All subjects answered a questionnaire and a semi-structured interview for collection of clinical data and headache characteristics.

A total of 161 migraine subjects were screened for inclusion. Further exclusion and drop out is described in Figure 1. One subject was excluded for not being adherent to sleep instructions. Two migraine subjects had no ppTMS recordings due to a technical malfunction of the coil thermostat. Thus, a total of 54 migraine patients (Table 1) were examined. We have previously reported data from the interictal phase compared to controls from the same study (20).

Study design

The study had a crossover design (Figure 2a) with one training day and two examination days. The training day was utilised for the subjects to become familiar with the laboratory and TMS examination and preceded the first examination by at least three days. The subjects were randomised to have the first examination day preceded by either two nights of eight-hour habitual sleep or two nights of four-hour restricted sleep. The randomisation was done in blocks within the migraine group by a research nurse (GBG, MSS) not involved in the examinations or analyses. The second examination day was preceded by the opposite sleep condition and scheduled at least seven days after the first examination. The investigator (MSM) was blinded for sleep condition and migraine diagnosis both during examinations and during data analysis. Examinations were performed by an investigator who did not know whether the subjects had a migraine diagnosis. Participants were also repeatedly told by a research nurse to not reveal their sleep condition and reminded in SMS notifications. Both examinations started at the same time of day for the same subject, either at 08:00 am or 10:30 am. Participants were instructed to plan their sleep time to wake up as close to 07:00 am as practically possible. Participants kept a headache diary from one week before, until one week after examinations. They marked the time of start and end of migraine headache and were allowed to use acute medication during the attack. They also filled in a sleep diary and used actigraphy throughout the examination period. The diaries used are previously described by our group (23).

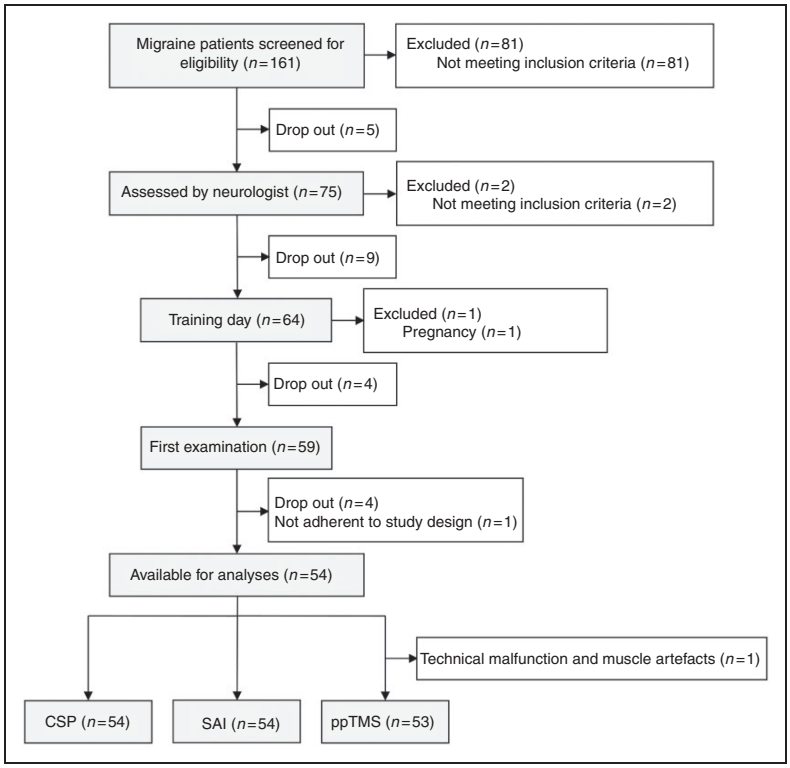

Figure 1. Inclusion and exclusion flow chart. Flow chart describing initial number of eligible subjects and further drop out and exclusion throughout the study period.

Table 1. Demographic and clinical data of 54 migraine subjects with two examinations divided into partially overlapping phase groups.

	Interictal phase[1] *(n = 46)*	Preictal phase[1] *(n = 10)*	Ictal phase[1] *(n = 16)*	Postictal phase[1] *(n = 7)*
Women/men	41/5	8/2	14/2	6/1
Age (years)	37.5 (11.2)	39.6 (12.5)	37.9 (10.4)	36.6 (12.9)
Right-/left-handedness[2]	42/4	10/0	14/2	6/1
MwoA/MA	27/19	9/1	8/8	3/4
NSM/SM	32/14	7/3	11/5	5/2
Habitual sleep/sleep restriction[3]	35/33	5/6	9/10	3/4
Migraine usual duration (h)	21.6 (22.1)	26.3 (25.4)	22.4 (21.3)	16.9 (21.5)
Migraine attacks/month last 6 months (1–4)[4]	2.2 (0.4)	2.0 (0.0)	2.3 (0.4)	2.4 (0.5)
Migraine usual intensity (1–4)[5]	2.6 (0.5)	2.5 (0.5)	2.6 (0.5)	2.4 (0.5)
Headache history (years)	21.4 (11.6)	22.5 (13.6)	21.9 (11.2)	18.7 (13.3)
Allodynia score (0–24)[6]	4.7 (4.6)	4.8 (4.7)	4.2 (3.7)	5.0 (3.5)
Photophobia (0–3)[7]	2.5 (0.7)	2.6 (0.5)	2.6 (0.7)	2.4 (0.8)
Phonophobia (0–3)[7]	2.2 (0.9)	2.2 (1.0)	2.4 (0.7)	2.3 (0.8)
Osmophobia (0–3)[7]	1.6 (1.2)	1.8 (1.4)	1.7 (1.3)	2.1 (0.9)
Sleep time (habitual) (min)[8]	452.9 (35.8)	451.2 (19.2)	474.3 (35.6)	471.0 (11.1)
Sleep time (restricted) (min)[8]	258.8 (41.5)	233.2 (14.4)	259.3 (40.5)	234.8 (9.4)

The table display data as mean (SD) or number of participants, for subjects with at least one recording in the corresponding phase (n). Paired pulse transcranial magnetic stimulation was performed for 2 less interictal subjects and 1 less ictal subject than the number indicated for each phase in the table. MwoA, migraine without aura; MA, migraine with aura; NSM, non-sleep related migraine; SM, sleep related migraine; NA, not applicable.
[1]Migraine patients with at least one recording in the corresponding phase using a 24-hour cut off.
[2]Self reported preferential use of one hand.
[3]Number of examinations following either habitual sleep or restricted sleep nights from a total of 105 included examinations.
[4]Categories: 1 = less than 1 per month, 2 = 1–3 per month, 3 = 4–5 per month, 4 = 6 or more per month.
[5]Categories: 1 = light – can keep doing a task, 2 = moderate – can do light tasks, 3 = strong – have to lie down, 4 = extremely strong – cannot lay still.
[6]Allodynia score (ASC-12) during usual migraine attacks.
[7]Symptom in migraine attacks not medically treated: 0 = no symptom, 1 = to a small degree, 2 = to a medium degree, 3 = to a strong degree.
[8]Mean sleep time for the two sleep-controlled nights for each sleep condition from actigraphy recording. Three examination days had missing actigraphy data and was replaced with sleep diary registrations.

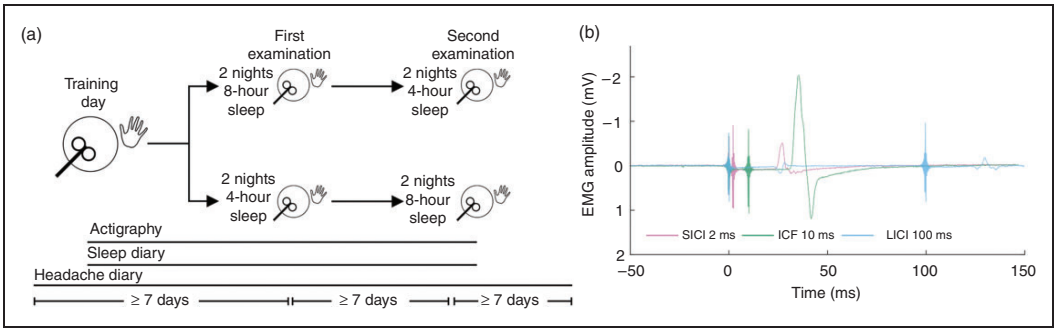

Figure 2. Study design. (a) Schematic overview of the crossover study design. Each subject participated in a training day preceding the first examination by at least three days. Subjects were block-randomised to have the first examination preceded by either two nights of habitual eight-hour sleep or restricted four-hour sleep. The second examination followed at least seven days after the first examination and was preceded by the remaining sleep condition. All subjects kept a headache diary from one week before until one week after examinations. Every subject registered sleep by both a sleep diary and a wrist-worn actigraph from the training day until the second examination and (b) Examples of single recordings of short-interval intracortical inhibition (SICI) with 2 milliseconds (ms) interstimulus interval (ISI), intracortical facilitation (ICF) using 10 ms ISI and long-interval intracortical inhibition (LICI) using 100 ms ISI. Conditioning stimuli (CS) was elicited at time 0 ms.

Transcranial Magnetic Stimulation

Subjects sat comfortably during examinations with their arms resting on a pillow. We used a figure-of-eight coil type MCF-B65 with a MagPro X100 stimulator with MagOption (MagVenture A/S, Farum, Denmark). Pulses were biphasic and 280 µs, initially inducing anteroposterior current in the tissue. We recorded electromyography (EMG) from the right abductor pollicis brevis muscle (APB) with Ag/AgCl electrodes through a Dual Bio Amp and a PowerLab 8/35 (ADInstruments, Dunedin, New Zealand). The left hemisphere was stimulated in all participants. Data were recorded in LabChart software version 8 (ADInstruments, Dunedin, New Zealand) with sampling rate 10 kHz, high pass 1 Hz and low pass 2 kHz. Navigation was used to adhere to a determined location using Localite TMS Navigator (Localite GmbH, Bonn, Germany). We stimulated the median nerve for SAI using a Digitimer Constant Current Stimulator model DS7A (Digitimer, Welwyn Garden City, United Kingdom) with 200 µs square wave-pulses.

The TMS protocol started with mapping of the location over contralateral motor cortex eliciting the largest and most consistent peak-to-peak motor evoked potential (MEP) amplitude in the APB. This location was marked in the Localite software and used for the rest of the TMS session. On the training day 70% of maximal stimulator output was used for mapping, while 120% of resting motor threshold (RMT) from the training day was used for mapping during the following examination days.

To determine RMT, we started using 35% of maximal stimulator output and increased intensity by 5% until MEPs were consistently measured above 50 µV. Then, we gradually reduced the stimulation intensity by 1% and used the last intensity eliciting MEP above 50 µV in five or more out of ten stimulations as RMT.

CSP was measured from the APB during isometric thumb abduction of about 50% maximum voluntary contraction against a Velcro band. Six measurements were collected using 120% RMT and 12 second intervals. Contraction level was assessed using visual assessment of EMG activity.

Paired pulse TMS was recorded in one continuous session. We recorded single test stimuli (TS) of 120% RMT, SICI and ICF with 80% RMT as conditioning stimulus (CS) and 120% RMT as TS, and LICI with 109% RMT as CS and 120% RMT as TS (Figure 2b). Interstimulus intervals (ISI) of 2 and 4 ms were used for SICI, 8 and 10 ms for ICF and 100 ms for LICI. The order of these stimulation types was randomised in blocks containing one of each type with randomised four, five or six seconds between each paired pulse train. Twenty blocks were recorded continuously, giving 20 recordings of single test stimuli and each paired stimulation type, and adding up to 120 recorded responses in total.

Alternating 20 single 120% RMT TMS stimulations and 20 SAI were measured using 21 ms ISI and TS of 120% RMT TMS intensity. The lowest median nerve stimulation intensity inducing a visible muscle twitch in APB was used as CS.

Data analysis

EMG recordings were filtered (1 Hz–2.5 kHz) in LabChart and motor evoked potential (MEP) peak-to-peak amplitudes were manually marked by an investigator (MSM) blinded for sleep condition and migraine phase (Figure 2b). LabChart was also used to rectify EMG for CSP analyses.

We used MATLAB R2019b (MathWorks, Natick, MA, USA) with custom scripts to average the rectified EMG for CSP. CSP onset was determined using the onset of MEP, defined as the first data point of the MEP which exceeded the upper limit of the mean consecutive difference threshold method (24). CSP offset was defined as the first data point above the lower limit with 50% or more of the following 5 ms above the same limit. Breakthrough EMG was manually defined by a blinded investigator (MSM) and included in the CSP.

The two examinations of each subject were evaluated for inclusion into the primary analyses of time to the next attack and time from the last attack. Time to the next and time from the last attack for each examination were determined using headache diaries. Time to the next attack was defined as time until reported start of migraine headache. Time from the last attack was defined as starting from the reported end of migraine headache. Examinations with more than seven days without attacks were set to 168 hours. Five examinations (1 time from attack; 4 time to attack) could not be included because of insufficient headache diaries. Ictal examinations were not included in either of the analyses. Preictal (24 hours before attack) and postictal (24 hours after attack) examinations were not included in the time from attack analysis and to attack analysis, respectively. After exclusions, 48 migraine patients for CSP (74 examinations; 38 habitual sleep and 36 sleep restriction), 48 migraine patients for SAI (73 examinations; 38 habitual sleep and 35 sleep restriction) and 46 migraine patients for ppTMS (69 examinations; 34 habitual sleep and 35 sleep restriction) were available for time from attack analyses. For time to attack analyses, 46 migraine patients for CSP (75 examinations; 37 habitual sleep and 38 sleep restriction), 46 migraine patients for SAI (74 examinations; 37 habitual sleep and 37 sleep restriction) and 45 migraine

patients for ppTMS (72 examinations; 35 habitual sleep and 37 sleep restriction) were available.

For secondary analyses, examinations were classified as interictal, preictal, ictal or postictal using a 24-hour cut off from the beginning or end of migraine headache according to the headache diary. We applied this 24-hour limit as in previous studies (23,25), because characteristics of the preictal phase are rather specific to this period preceding the ictal phase (26). The preictal phase started 24-hours prior to the reported start of migraine headache. The ictal phase lasted from the start of migraine headache until the end of migraine headache. The postictal phase lasted until 24-hours after the end of migraine headache. Examinations were allocated to the phase the subjects were in when the examination was performed. Examinations performed during overlapping preictal and postictal phases were excluded. Each phase was compared to the interictal phase, and all four phases were included in the same model.

Statistical analysis

We performed statistical analyses in STATA version 17.0 (StataCorp LP). We included CSP duration and every ppTMS and SAI peak-to-peak amplitude in separate linear mixed models for each of the different TMS-responses. Linear mixed models are well suited to handle missing data for when subjects had recordings of different sleep conditions in different phases and is commonly applied for repeated measurements (20,27). Every analysis was performed with an intention to treat basis with intended sleep as sleep condition. Actual sleep duration was recorded with actigraphy (except for three examination days where sleep diary replaced missing data) and is described in Table 1. To better meet assumptions of normality in residuals, the peak-to-peak amplitudes were transformed to the power of 0.2. Box cox transformation was applied to find the most appropriate transformation for normality. We used the model design with the lowest Akaike and Bayesian information criterion (AIC/BIC) values between different theoretically appropriate random intercept and random slope models with the same variables.

The model chosen for primary analysis of CSP was a 2- level random intercept model with time to/from attack, sleep condition and their interaction as fixed effects and subject as level 2. The interaction effect represents difference between sleep conditions in the slope of CSP duration over time. The models chosen for the analyses of ppTMS and SAI were 3-level models with stimulation type, time to/from attack, sleep condition and their interactions as fixed effects, and subject and stimulation type as random intercepts at level 3 and 2, respectively, with time to/from attack as random slope at level 3. Test stimuli, time = 0 and habitual sleep were used as bases in the model. Stimulation type represents the difference between peak-to-peak amplitudes of test stimuli and conditioned stimuli. We conducted separate models for each of the ppTMS stimulation types (SICI 2 ms, SICI 4 ms, ICF 8 ms, ICF 10 ms and LICI 100 ms). The interaction effect in ppTMS and SAI models represent the difference between sleep conditions in the slope of stimulation type differences over time.

We performed secondary analyses replacing time in the model with migraine phase with a 24-hour cut off from start and end of migraine headache. The interictal phase was the base in the model. Post hoc contrasts are reported for habitual sleep separately between phases. Due to the restricted number of individuals in the different phases of the secondary analyses, we applied restricted maximum likelihood estimation with the Kenward-Roger Degrees of Freedom approximation.

We investigated significant findings in primary analyses for correlation with clinical parameters in exploratory analyses. Clinical variables from a questionnaire were included in the model as a fixed effect interacting with the significant interaction. We assessed attacks per month, usual attack duration and usual migraine headache intensity. We report two-sided p-values <0.05 as significant.

The study size was originally planned for a larger migraine group to account for spread of examinations throughout the migraine cycle. By assessing 75 includable subjects we hoped to have 60 subjects completing the study and about 45–50 interictal subjects. Two-tailed Student's t-test comparing e.g., 30 controls and 45 patients with alpha 0.05 would then have 80% power to detect a medium to large Cohen's d effect size of approximately 0.67. We did not perform a priori power calculations for analyses of temporal relations to attack or phase comparisons within the migraine group.

Results

Demographic and clinical data are presented in Table 1. Recorded sleep duration is distributed between sleep conditions as expected from the study design.

The average time from examination to the next attack was numerically shorter after sleep restriction (87.0 hours; SD 61.6) compared to habitual sleep (105.6 hours; SD 64.0). The average time from the last attack to the next examination was more similar between sleep restriction (121.6 hours; SD 55.7) and habitual sleep (110.1 hours; SD 60.0).

After a migraine attack

After sleep restriction, SICI 2 ms was reduced with shorter time elapsed since the previous migraine attack (Figure 3). This was seen as a significant interaction effect of *time* × *sleep* × *SICI 2 ms* ($p = 0.041$; Table 2). In secondary analyses, SICI 2 ms was also reduced after sleep restriction in the postictal compared to the interictal phase ($p = 0.013$; Table 3; Figure 4).

There were no significant effects of time after the previous attack and sleep restriction on the other TMS-measures ($p > 0.15$; Table 2). However, comparing the postictal and interictal phase in secondary analyses we also found an increase of both ICF 8 ms ($p = 0.003$; Table 3; Figure 4) and ICF 10 ms ($p = 0.021$; Table 3; Figure 4) after sleep restriction postictally.

Before a migraine attack

After sleep restriction, LICI 100 ms increased with time closer to the next migraine attack (Figure 5). We saw this as a significant interaction effect of *time* × *sleep* × *LICI* ($p = 0.006$; Table 2). This interaction was significantly affected by usual migraine headache intensity ($p = 0.002$; 95% CI 0.0008 to 0.003), where subjects with higher usual intensity had a larger LICI increase after sleep restriction closer to the attack start. In secondary analyses, we also observed that LICI increased after sleep restriction in the preictal phase compared to the interictal phase ($p = 0.034$; Table 3; Figure 4). The post hoc contrast effect of *preictal/interictal phase* × *LICI* was significant after habitual sleep ($p = 0.007$; 95% CI 0.03 to 0.19), indicating that it was the LICI effect after habitual sleep that was reduced preictally.

A reduction of the SAI-effect with time closer to the next migraine attack was seen after sleep restriction (Figure 5). This was found to be a significant interaction effect of *time* × *sleep* × *SAI* ($p = 0.026$; Table 2).

We did not observe any significant interaction effects on SICI 2 and 4 ms, ICF 8 and 10 ms or CSP before migraine attacks ($p > 0.44$; Table 2).

No other significant interaction effects were found between attacks per month, usual attack duration, usual migraine headache intensity and the TMS-measurements with significant primary interaction effects ($p > 0.10$).

Discussion

This study shows that the effect of sleep restriction on TMS-measures of cortical excitability may vary within the migraine cycle and specifically with time to the next attack or from the previous migraine attack. After an attack, the SICI 2 ms inhibitory effect was more

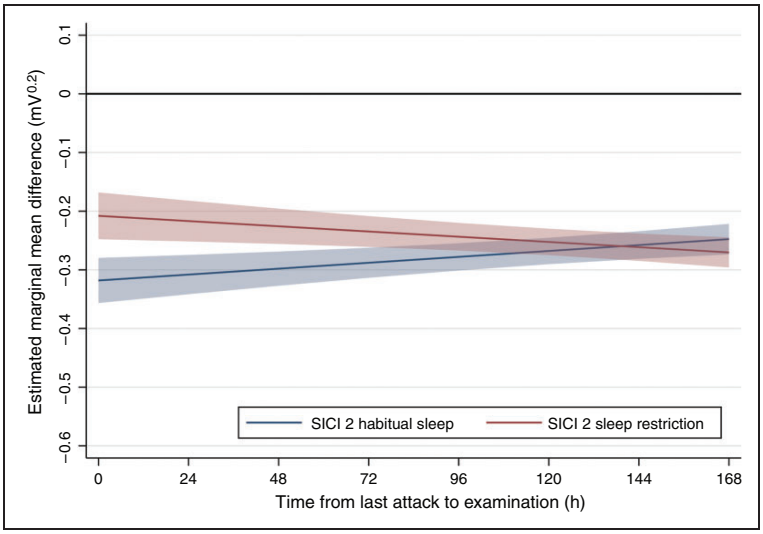

Figure 3. Estimated marginal mean difference of the significant effect after attacks. Line plots represent estimated marginal mean difference between peak-to-peak MEP amplitude millivolts to the power of 0.2 ($mV^{0.2}$) after test stimuli and conditioned stimuli for short-interval intracortical inhibition (SICI) at 2 ms. The marginal mean difference is displayed separately for habitual sleep and sleep restriction and over time from the end of a migraine attack until 168 hours after the attack. Marginal mean differences are calculated from linear mixed models. The shaded area indicates estimated marginal standard error. The interaction effect *time* × *sleep* × *SICI 2 ms* was significant ($p = 0.041$).

Table 2. Interaction effects of sleep and temporal relation to migraine attacks on TMS-measurements.

	n	z-statistic	p-value	Coefficient	95% CI	
Time from attack to examination (h)						
CSP	48	−1.21	0.23	−0.14	−0.38	0.09
SICI 2	46	−2.05	**0.041***	−0.0008	−0.002	−0.00003
SICI 4	46	−0.78	0.44	−0.0003	−0.001	0.0005
ICF 8	46	−1.23	0.22	−0.0004	−0.001	0.0002
ICF 10	46	−1.45	0.15	−0.0005	−0.001	0.0002
LICI 100	46	0.50	0.62	0.0002	−0.0006	0.001
SAI	48	0.88	0.38	0.0003	−0.0004	0.001
Time from examination to attack (h)						
CSP	46	0.03	0.98	0.002	−0.15	0.15
SICI 2	45	−0.77	0.44	−0.0002	−0.0008	0.0003
SICI 4	45	−0.03	0.98	−0.000008	−0.0005	0.0005
ICF 8	45	−0.68	0.50	−0.0002	−0.0006	0.0003
ICF 10	45	−0.56	0.57	−0.0001	−0.0006	0.0004
LICI 100	45	2.77	**0.006***	0.0009	0.0002	0.001
SAI	46	−2.22	**0.026***	−0.0006	−0.001	−0.00007

Results from the interaction *time to/from examination from/to attack × habitual sleep/restricted sleep (× stimulation type (ppTMS and SAI))* in linear mixed models, including number of subjects (n), z-test statistic, p-value, the coefficient and 95% confidence intervals (CI) for difference in stimulation types between sleep conditions per time point (h). CSP, cortical silent period; ICF, intracortical facilitation; LICI, long-interval intracortical inhibition; ppTMS, paired pulse transcranial magnetic stimulation; SAI, short-latency afferent inhibition; SICI, short-interval intracortical inhibition; TMS, transcranial magnetic stimulation. The asterisk (*) and bold text indicate $p < 0.05$.

reduced by sleep restriction the shorter the time that had elapsed from the attack. SICI 2 ms was also reduced after sleep restriction in the postictal compared to the interictal phase in secondary analyses. We found no effects on ICF in the primary analyses, but ICF was increased after sleep restriction in the postictal phase. In the time leading up to an attack we found an increasing LICI inhibitory effect and a decreasing SAI inhibitory effect after sleep restriction the shorter the time that remained until the commencement of the attack. Subjects with higher than usual attack intensity had a greater LICI increase. In secondary analyses, LICI was also more increased after sleep restriction in the preictal compared to the interictal phase, and LICI after habitual sleep was lower preictally compared to the interictal phase.

GABA-A and glutamatergic alterations following migraine attacks

Our findings indicate that sleep restriction induced a larger decrease in GABA-A mediated inhibition in the postictal phase and the shorter the time that had elapsed from the previous migraine attack. We found this effect as changes in SICI which is understood to represent short lasting inhibitory post synaptic potentials from $\alpha 2$ or $\alpha 3$ subtype GABA-A receptor activation, possibly representing a low-threshold cortical inhibitory circuit. This inhibitory effect is thought to be modulated by presynaptic GABA-B mediated autoinhibition of inhibitory interneurons, to be increased by dopamine and nicotine, and to be decreased by noradrenaline (21,28). We also found indications of postictally increased ICF after sleep restriction. ICF represents excitability of excitatory circuits in the cortex; probably as a net facilitation from glutamatergic NMDA-receptor activation and GABA-A receptor mediated inhibition as in SICI (21,29), with contribution from subcortical mechanisms (30).

Previous studies of SICI and ICF after sleep deprivation in healthy subjects have found a reduced SICI inhibitory effect and increased ICF (31,32). This response is thought to accompany a lack of sufficient desaturation of synaptic potentiation by insufficient sleep, which leads to alterations in neuroplasticity and can also compromise learning, memory and attention (32). Thus, migraine patients may display an exaggerated effect of reduced sleep on neurological functioning or a susceptibility to these effects at milder levels of insufficient sleep shortly after the attack. It is well known that most migraine patients are forced to sleep during attacks at least occasionally (6), and that sleep is an effective treatment for migraine headache (4). Sleep restriction before the recordings soon after the attack in this study probably occurred during the ictal phase. Consequently, we propose that sufficient sleep during migraine attacks is of direct importance for maintaining neurological functioning in migraine patients.

Table 3. Interaction effects on outcome variables for sleep condition and each migraine phase compared to the interictal phase.

Phase	t	p	95% CI	
Preictal				
SICI 2 ms	0.42	0.67	−0.08	0.12
SICI 4 ms	0.53	0.60	−0.07	0.13
ICF 8 ms	0.64	0.52	−0.06	0.12
ICF 10 ms	−0.28	0.78	−0.10	0.08
LICI 100 ms	−2.12	**0.034***	−0.22	−0.009
SAI 21 ms	1.23	0.22	−0.03	0.15
CSP	0.12	0.90	−34.5	39.1
Ictal				
SICI 2 ms	−0.10	0.92	−0.08	0.08
SICI 4 ms	0.09	0.93	−0.07	0.08
ICF 8 ms	0.78	0.43	−0.04	0.10
ICF 10 ms	0.75	0.46	−0.04	0.10
LICI 100 ms	−0.28	0.78	−0.10	0.07
SAI 21 ms	−1.33	0.18	−0.13	0.02
CSP	0.42	0.68	−22.5	34.4
Postictal				
SICI 2 ms	2.50	**0.013***	0.04	0.33
SICI 4 ms	0.11	0.91	−0.14	0.16
ICF 8 ms	3.03	**0.003***	0.07	0.32
ICF 10 ms	2.31	**0.021***	0.02	0.28
LICI 100 ms	1.31	0.19	−0.05	0.27
SAI 21 ms	−0.47	0.64	−0.16	0.10
CSP	1.67	0.99	−8.1	92.3

Results from the interaction *sleep restriction/habitual sleep* × *phase* (× *stimulation type (ppTMS and SAI))* in random intercept models of paired pulse transcranial magnetic stimulation (ppTMS), short-latency afferent inhibition (SAI) and cortical silent period (CSP). Test statistic for small sample sizes (t), p-value (p) and 95% confidence intervals (CI) are displayed. The dependent variable of ppTMS and SAI was motor evoked potential (MEP) amplitude in millivolt (mV) which was transformed to the power of 0.2. The dependent variable for CSP was CSP duration in milliseconds (ms). Number of examination days included in the analysis was (CSP and SAI/ppTMS): Interictal 68/63, preictal 11/11, ictal 19/18, postictal 7/7. The included ppTMS types were: Short-interval intracortical inhibition (SICI), intracortical facilitation (ICF) and long-interval intracortical inhibition (LICI). Each measurement is displayed with the corresponding interstimulus interval (ISI). We used separate models for each stimulation type. All four migraine phases were included in every model. The total number of individuals in each model was 54 for CSP and SAI, and 53 for ppTMS.
The asterisk (*) and bold text indicate $p < 0.05$.

GABAergic and cholinergic changes in the period leading up to migraine attacks

We have previously reported decreased CSP duration after sleep restriction in interictal migraine patients compared to controls (20). This finding may be related to the gradually increasing inhibitory LICI effect after sleep restriction leading up to a migraine attack that we observed in this study. LICI is thought to represent slow inhibitory post synaptic potentials acting through GABA-B receptors, which is understood to be dependent on the availability of GABA in the synaptic cleft. GABA-B receptor mediated inhibition is also a mediator of the CSP effect and presynaptic GABA-B receptors may be relevant for these inhibitory effects by regulating the amount of GABA available in the synapse (21,33,34). CSP requires higher levels of GABA availability than LICI before the inhibitory effect is saturated. Thus, presynaptic GABA-B activity may reduce CSP duration without affecting LICI (33). CSP and LICI also differ in the way that CSP possibly represents duration of inhibition, where LICI represents the magnitude of inhibition (34). Shortened CSP has previously been observed as the LICI effect increases (35) and increased CSP has been observed with a concurrent decline in LICI during exercise induced fatigue (33). Thus, our results imply that while the temporal aspect of GABA-B mediated inhibition is decreased by sleep restriction in the interictal phase, the magnitude of inhibition may be elevated by sleep restriction closer to the attack or in the preictal phase specifically. This preictal increase in GABA-B magnitude may occur concurrently with a stable deficit in cortical inhibitory duration as we did not discover changes in CSP towards the start of an attack. While this underlying dysfunction represented by altered CSP was associated with both premonitory and ictal hypersensitivity (20), the LICI change was associated with increased usual attack intensity. Thus, suggesting a closer link between headache and this preictal GABA-B inhibitory affection.

The preictally decreased LICI after habitual sleep (Figure 4) may be in coherence with the theory that migraine patients have increased thresholds for inhibitory homeostatic responses in the preictal phase (36), which may be related to hypoexcitability measured at rest (12,14). This model may also be in line with observations of preictal hyperresponsiveness in previous studies (10,14). indicating an involvement of slow GABA-B receptor mediated inhibition. Inhibitory thresholds may be comparable to interictal levels in examinations after sleep restriction due to sleep deficit induced increase of cortical activity (32,36).

Circadian rhythm related alterations of GABA-B receptor mediated inhibition of motor cortex have been linked to corticotropin-releasing hormone (CRH) from the paraventricular nucleus (PVN) of hypothalamus. GABA-B mediated inhibition decreases during the day, and previous studies suggest that CRH modulates GABAergic neurons postsynaptically on different levels of the central nervous system (37). CRH also contributes to regulation of spontaneous waking (38) and reduced CRH after sleep deprivation has been suggested to mediate temporary relief of depression observed after sleep deprivation (39). Our group has previously described how migraine subjects

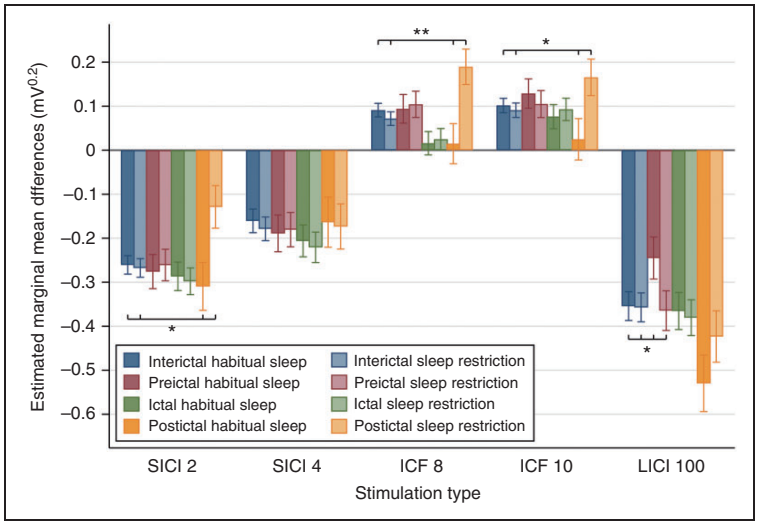

Figure 4. Paired pulse transcranial magnetic stimulation. Estimated marginal mean differences between test stimuli and conditioned stimuli from linear mixed models of paired pulse transcranial magnetic stimulation (ppTMS) in millivolts to the power of 0.2 ($mV^{0.2}$). The x-axis displays paired pulse stimulation type with corresponding interstimulus intervals (ISI) in ms. Separate statistical models were applied for each stimulation type and each model included all four migraine phases. Stimulation types were short-interval intracortical inhibition (SICI), intracortical facilitation (ICF) and long-interval intracortical inhibition (LICI). Positive values represent facilitation and negative values represent inhibition. Error bars indicate estimated marginal standard error. Statistical significance bars represent interaction effects of *sleep restriction/habitual sleep* × *phase* × *stimulation type*. Asterisks mark significance level: $^{*}p < 0.05$, $^{**}p < 0.01$.

in the preictal phase display increased sleepiness compared to the interictal phase (40). A dysfunction of PVN and CRH related mechanisms preictally in migraine patients, where CRH release may be more increased in the morning despite foregoing sleep restriction, may be one explanation for increased LICI after sleep restriction closer to the start of an attack as seen in this study.

Cell bodies of PVN also control yawning, which is a common premonitory symptom of migraine patients (41–43), indicating that this nucleus may be relevant for the period prior to attacks. Yawning can also be induced in rats by activating oxytocinergic neurons from PVN to ventral tegmental area, hippocampus and amygdala, parallel to an observed extracellular dopamine increase in the shell of nucleus accumbens (43). Dopaminergic input to the accumbens shell may arise from the dorsal raphe nucleus (44). Schulte et al. reported enhanced functional connectivity between nucleus accumbens and dorsal pons including the dorsal raphe nucleus, as well as left amygdala and hippocampus in the preictal phase (8). Accordingly, central nervous networks with altered preictal function (8) may be related to hypothalamic systems that produce both premonitory symptoms and the sleep related alterations of cortical excitability seen in the present study.

Finally, the effect of SAI which was more reduced by sleep restriction closer to the start of attacks, is likely both mediated by cholinergic input from thalamus to the cortex and by α1 subunits of GABA-A receptors (21,45). Previous findings of preictally reduced rapid eye movement sleep (REM) density in migraine may indicate impaired cerebral cholinergic input during sleep (46). Sleep deprivation may also induce a reduction in cortical levels of acetylcholine in humans (47). Consequently, migraine patients may have a subtle cortical cholinergic deficit which is exaggerated by insufficient sleep demonstrated by a reduction of the SAI inhibitory effect closer to the migraine attack commencement.

Strengths and limitations

We utilised a study design which was randomised and blinded. The investigator was blinded to whether the participants were migraine patients or controls (not included in these analyses), where in the migraine cycle the subjects where and how much they had slept before examinations. This blinding was kept throughout data analyses.

We chose 24 hours as a cut off limit for excluding the preictal and postictal phase from each of the two

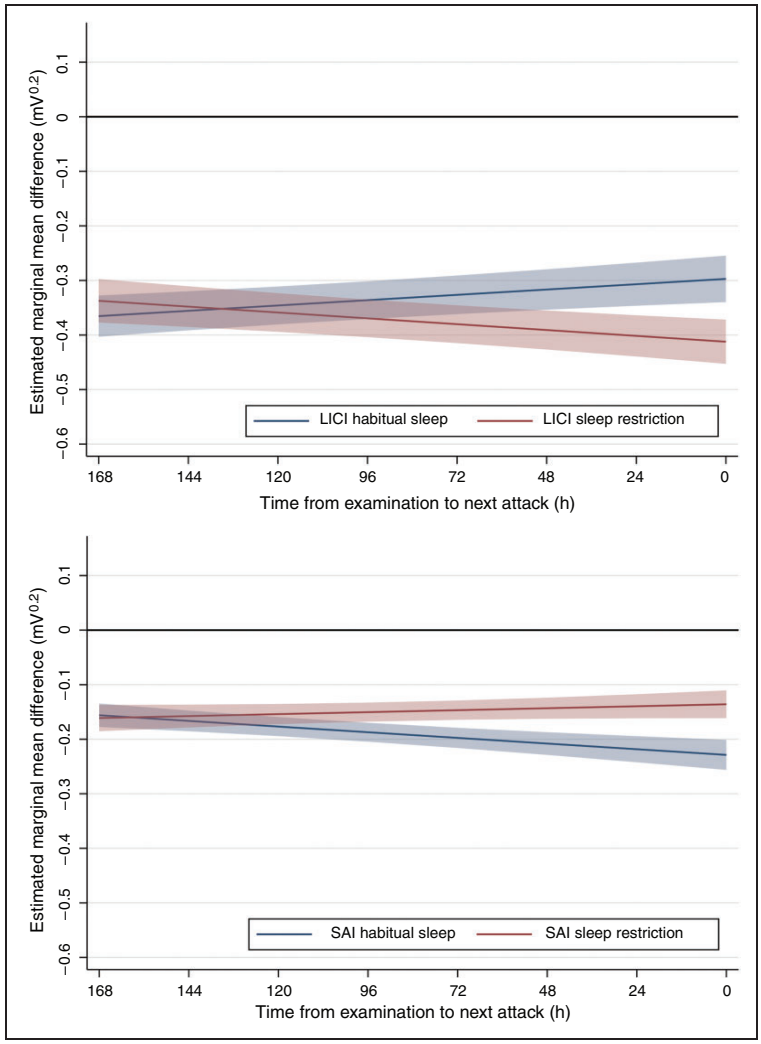

Figure 5 Estimated marginal mean differences of the significant effects before attacks. Line plots represent estimated marginal mean difference between peak-to-peak MEP amplitude millivolts to the power of 0.2 ($mV^{0.2}$) after test stimuli and conditioned stimuli for long-interval intracortical inhibition (LICI) and short-latency afferent inhibition (SAI). The marginal mean difference is displayed separately for habitual sleep and sleep restriction and over time from 168 hours before a migraine attack and up to the attack onset at time 0. Marginal mean differences are calculated from linear mixed models. The shaded area indicates estimated marginal standard error. The interaction effects *time* × *sleep* × *LICI* ($p = 0.006$) and *time* × *sleep* × *SAI* ($p = 0.026$) were significant.

separate analyses in this study. However, the exact duration of these phases is currently unknown and may vary between subjects. Some previous findings implicate a possible duration of 48 hours for the preictal phase (16). Thus, by this extended definition, some preictal properties may have been included in the analyses of effects after attacks.

Caffeine consumption was not allowed prior to the examinations in this study. This leaves a possibility for withdrawal effects as a confounding factor with unknown effects on cortical excitability.

Most participants reported in a questionnaire to have between one to three attacks per month and a large portion to have between four to five attacks

per month for the past six months. Thus, the study population represents episodic migraine patients with an active disease. However, some subjects had a rather low attack frequency.

The phase-grouped secondary analyses only have a posteriori sample sizes sufficient to evaluate large effect sizes, particularly for the postictal recordings. Consequently, smaller effects of these variables may have remained undetected. The chance of detecting effects occurring at random is also greater with small sample sizes. We applied the Kenward-Roger approximation designed to improve the performance of complicated tests of fixed effects in small samples. However, the results of the secondary analyses should only be considered as preliminary, especially when not in accordance with the findings in the primary analyses. The significant findings in the primary analyses for SICI and LICI, but not SAI, had supporting findings in the secondary analyses. Because there were no significant findings for ICF in the primary analyses, the findings for ICF in the postictal phase in the secondary analyses should be considered preliminary.

We observed some numerical differences between the time to attacks and from attacks for the different sleep conditions. Whether these differences occur because sleep changes trigger attacks in some subjects is unknown. It is also uncertain whether subsequent sleep changes or sleep recovery following sleep restriction could affect attack initiation. However, there was no difference in number of preictal or ictal recordings following the two sleep conditions. Thus, we suggest that effects of the different sleep conditions on attack onset were absent or only applicable to a small subset of participants in this study.

Conclusion

We have revealed different effects of sleep restriction on cortical excitatory/inhibitory balance during the course of the migraine cycle. Our findings imply sleep-wake related mechanisms as part of the migraine cycle pathophysiology. Before and close to the start of an attack, we found increased GABA-B receptor mediated inhibition after sleep restriction. This effect may be related to alterations in mechanisms of circadian rhythm in the hypothalamus and may connect previous findings of altered cortical inhibitory capability and hypothalamic dysfunction. We also found reduced cholinergic mediated GABA-A inhibition after sleep restriction before and close to the start of an attack. This finding may indicate a cholinergic dysfunction prior to attacks which may be related to sleep architecture. Shortly after an attack, we observed a decrease of GABA-A mediated inhibition after sleep restriction. This effect may indicate that sufficient sleep during the migraine attack is of increased importance for maintaining normal neurological functioning in migraine patients.

Article highlights

- Insufficient sleep gradually increases GABA-B receptor mediated inhibition and reduces cholinergic modulated GABA-A inhibition towards the start of a migraine attack.
- Insufficient sleep reduces GABA-A inhibition soon after a migraine attack, indicating that sufficient sleep may be of increased importance during migraine attacks to maintain normal neurological function.

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Authors' contributions

All authors have provided substantial contributions to the final version of the manuscript. MSM, MU, TS and PMO planned the study. MSM conducted the examinations, performed the data analysis, interpreted the data and wrote the first draft. MU, TS and PMO contributed to the data analysis and writing of the manuscript. LJS, EB, MSS and GBG evaluated subjects for inclusion and provided feedback on the manuscript.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the Regional Committee for Medical Research Ethics Central Norway. Written, informed consent was obtained from all participants.

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Paper III

Original Article

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Effects of insufficient sleep on sensorimotor processing in migraine: A randomised, blinded crossover study of event related beta oscillations

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Abstract

Background: Migraine has a largely unexplained connection with sleep and is possibly related to a dysfunction of thalamocortical systems and cortical inhibition. In this study we investigate the effect of insufficient sleep on cortical sensorimotor processing in migraine.

Methods: We recorded electroencephalography during a sensorimotor task from 46 interictal migraineurs and 28 controls after two nights of eight-hour habitual sleep and after two nights of four-hour restricted sleep. We compared changes in beta oscillations of the sensorimotor cortex after the two sleep conditions between migraineurs, controls and subgroups differentiating migraine subjects usually having attacks starting during sleep and not during sleep. We included preictal and postictal recordings in a secondary analysis of temporal changes in relation to attacks.

Results: Interictally, we discovered lower beta synchronisation after sleep restriction in sleep related migraine compared to non-sleep related migraine ($p = 0.006$) and controls ($p = 0.01$). No differences were seen between controls and the total migraine group in the interictal phase. After migraine attacks, we observed lower beta synchronisation ($p < 0.001$) and higher beta desynchronisation ($p = 0.002$) after sleep restriction closer to the end of the attack compared to later after the attack.

Conclusion: The subgroup with sleep related migraine had lower sensorimotor beta synchronisation after sleep restriction, possibly related to dysfunctional GABAergic inhibitory systems. Sufficient sleep during or immediately after migraine attacks may be of importance for maintaining normal cortical excitability.

Keywords

Headache, sleep deprivation, GABA, interictal, preictal, postictal

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Introduction

There is a well-known connection between migraine and sleep (1) and recent evidence points toward common underlying mechanisms for migraine pathophysiology and sleep physiology (2). Sleep disturbances are reported to trigger migraine attacks (1) and sleep is commonly used to abort migraine headache (3). Poor sleep has been associated with higher headache frequency in migraineurs (4) and short sleep time has been associated with central sensitisation and chronic migraine pain development (5) Consequently, it is of great interest to study the effects of insufficient sleep in

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migraine subjects to better understand how sleep-changes can predispose for attacks.

A dysfunctional thalamocortical system may cause cortical inhibitory deficits in motor and somatosensory systems in migraineurs during the interictal phase (6,7). Thresholds for inducing inhibitory mechanisms may be reduced in migraineurs between attacks, possibly to counterbalance cortical hyperresponsivity (8). Abnormal connectivity between thalamus and both the precuneus and the visual cortex has also been described (9). However, the brain dysexcitability suggested in migraine are probably not the same in different migraine subgroups (10).

Event related desynchronisation and synchronisation (ERD and ERS) are electrophysiological measures of changes in neuronal synchrony, that can be applied to evaluate interactions between thalamocortical systems and cortical interneurons (11,12). ERD/ERS can be calculated from the electroencephalogram (EEG), and are time-locked to an event and specific for frequency bands in the EEG. ERD/ERS in the beta frequency band over sensorimotor cortex during hand movements mostly reflect responses to afferent stimulation, but also motor generation (13,14). Sensorimotor beta-ERD is commonly referred to as movement related beta decrease (MRBD), while the increase in beta amplitude after movement cessation is often referred to as post-movement beta rebound (PMBR) (15). We have previously reported sensorimotor beta-ERD/ERS during a hand task with an integrated sensory discrimination task evaluated throughout the migraine phases (12,16), and the method appears relevant for evaluating migraine related cortical features.

Migraineurs can be divided into those with mostly sleep related attacks (e.g., sleep related migraine, SM) and subjects with non-sleep related migraine (NSM). Polysomnography recordings in migraineurs have revealed that SM have reduced sleep quality with increased number of awakenings while NSM have increased slow wave sleep, similar to what is seen after sleep deprivation in healthy subjects (17). In an experimental model of insufficient sleep, NSM subjects displayed a reduction of GABAergic cortical inhibition after about 50% sleep restriction (18). On the other hand, the traditional subgrouping of migraineurs with and without aura (MA and MwoA respectively) have not displayed differences in sleep disturbances (19). Whether MA and MwoA differ in objective measures of sleep is unknown and no definite pattern of differences in effects of sleep restriction have emerged so far (18).

We hypothesise that changes in the duration of sleep will affect cortical function differently in migraineurs, specific migraine subgroups and in different parts of the migraine cycle. The aim of this study was to investigate the association between migraine and insufficient sleep by measuring the effect of sleep restriction on beta-ERD/ERS during a sensorimotor task, which represent mechanisms previously implied in migraine pathophysiology (12,16). Our first objective was to evaluate whether sleep restriction would have different effects on beta-ERD and beta-ERS during a sensorimotor task between migraineurs and controls, and in different subgroups of migraineurs. We studied both sleep related subgroups (SM and NSM), and MA and MwoA. Our second objective was to evaluate whether effects of sleep restriction would depend on the time elapsed from the last migraine attack or the time to the next attack.

Methods

Subjects

We recruited migraine subjects and healthy controls between 18 and 65 years of age via social media and mass media. Nurses with experience in headache research screened all subjects using predefined criteria. A neurologist evaluated inclusion and exclusion criteria for migraine subjects in addition to a diagnosis of migraine with and/or without aura according to The International Classification of Headache Disorders, 3rd edition (20). Between one and six self-reported migraine attacks per month for the previous six months was required. Prophylactic migraine treatment was prohibited during the study period and four weeks before examinations. We excluded migraine patients with tension type headache for seven days or more per month. We used a questionnaire to prospectively exclude controls with bothersome non-migraine headache if they had headache at least once per month, had previously consulted a doctor or usually used medication for headache. Exclusion criteria for all subjects were sleep disorders, treated or severe hypertension, lung-, neurological or psychiatric disease affecting everyday function, infectious-, metabolic-, endocrine-, neuromuscular-, cerebrovascular-, neoplastic or connective tissue disease, other painful diseases, recent injury, symptomatic heart disease, epilepsy in close relatives, treatment with medications affecting neural, vascular or muscular function, pregnancy, previous craniotomy, alcohol or narcotics abuse and prophylactic allergy treatment. We asked participants to not exercise, consume caffeinated beverages or use tobacco on the same day as examinations.

We screened 161 migraine subjects and 72 healthy controls for inclusion. Drop out and exclusion are described in Figure 1a and b. Only examinations performed during the interictal phase with a 24-hour cut off from the start or end of migraine headache were included in the primary analyses. Thus, 46 migraine subjects

with at least one interictal examination (68 examinations) and 28 controls (55 examinations) were included.

We differentiated migraineurs by when their attacks usually start, as they reported in a questionnaire. SM was defined as those having migraine usually start "upon awakening" or "during the night, awakening them from sleep". NSM was defined as those having migraine usually start "during daytime before noon", "during daytime after noon" or at "no regular onset time".

The Regional Committee for Medical Research Ethics Central Norway approved the study. Written, informed consent was obtained from all subjects. All participants were remunerated with 900 NOK intended to cover expenses (about 90 EUR with current exchange rates).

Study design

Each participant was examined with EEG on three different days (Figure 1c). First, a training day was utilised for the subjects to become familiar with the tasks and procedures. We applied a crossover design for the following first and second examination day which were preceded by either two nights of habitual sleep (eight hours) or restricted sleep (four hours). The order of sleep conditions was randomised separately for migraineurs and controls. Both examinations were scheduled at the same time of the day for each participant, either at 08:00 am or 10:30 am. Participants recorded sleep duration with a wrist-worn actigraph (Actiwatch Spectrum, Philips Norge AS, Norway) and a sleep diary (21). Migraineurs filled in a headache diary (21) from one week before until one week after examinations. The investigator (MSM) was blinded for diagnosis and sleep condition during examination and data analyses.

Electroencephalography recording

Scalp EEG was collected using BrainVision 32-channel actiCap active electrodes and EasyCap (Brain Products GmbH, Germany) according to the extended international 10/20 system (22). with channels for horizontal and vertical eye movements and channels for wrist flexion and extension electromyography (EMG). Active EMG electrodes were placed on the muscle belly of the flexor carpi radialis muscle and the muscle belly of the extensor carpi radialis muscles which were most prominently contracted during the task. Reference electrodes were placed distally over the tendon proximal to the wrist. Channels were recorded

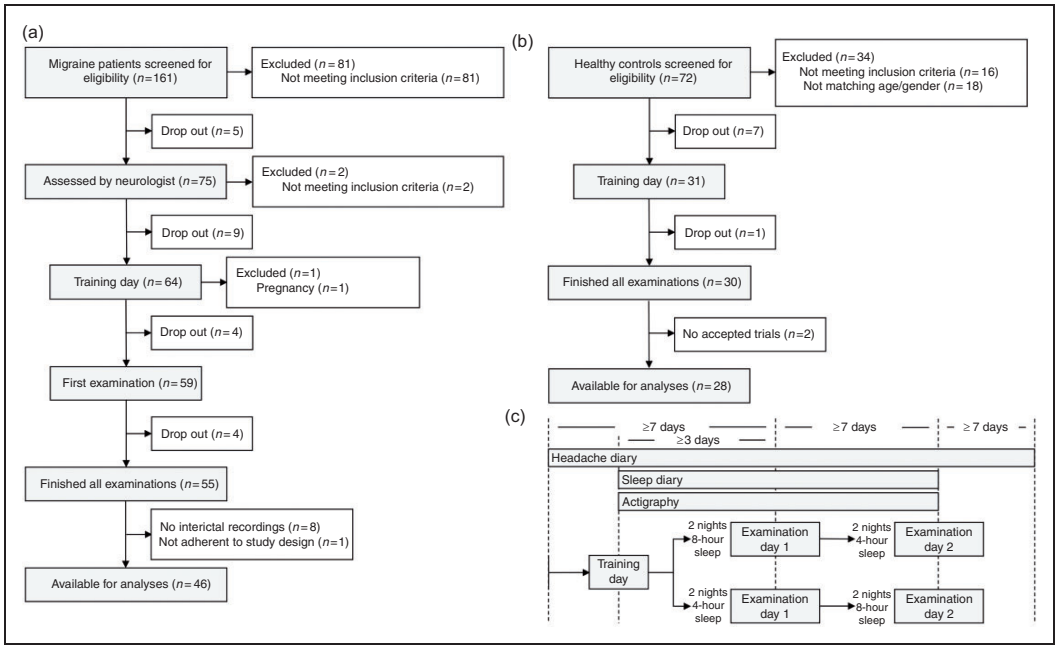

Figure 1. Inclusion and exclusion flow chart and study design, (a) and (b) show flow chart for the process of inclusion and exclusion, reporting number of participants (n) at every stage and (c) Study design chart depicting how every participant underwent one training day followed by two examination days. The examination days were preceded by either two nights of eight-hour habitual sleep or two nights of four-hour sleep restriction in randomised order. Every participant filled in a headache diary and a sleep diary and wore an actigraph to register sleep time.

with a reference at FCz and a common ground at FPz. EEG and EMG signals were amplified and digitised through a BrainAmp amplifier and recorded in the BrainVision recorder software (Brain Products GmbH, Germany) using 5000 Hz sampling rate, 1000 Hz low pass and 0.1 Hz high pass filter. Impedances were kept below 25 kOhm as is suitable for BrainAmp actiCap active electrodes with integrated active circuits for impedance conversion to allow high quality signals at higher impedance.

Sensorimotor task

Participants were lying comfortably on an inclined bed in an illuminated room with eyes open during examination. Their right arm was resting on a custom-made armrest behind a cover, making the participant unable to see their right hand. A screen in front of the participants alternated 40 times between red and green colour with randomised 15–18 second intervals and each colour change indicated for the participant to start the pre-rehearsed task. The task was self-paced, and the participants first flexed their wrist for two seconds, then extended their wrist for two seconds and then relaxed their arm. A small bowl rotating slowly was placed below their hand. The bowl contained small balls of Styrofoam, wood and rubber which were fixed to the bowl. During flexion, the fingers of the participants were in contact with the rotating balls. Participants were told that we would ask them after each session whether they noticed a ball of metal in the bowl to direct attention to the task and to introduce an element of sensory discrimination. We applied the same task in previous examinations of ERD/ERS (12,16).

Data analysis

EEG data was pre-processed in BrainVision Analyzer 2.2 (Brain Products GmbH, Germany). We first applied a 1–100 Hz IIR Butterworth filter and a 50 Hz notch filter, then applied cubic spline interpolation to change sampling rate to 512 Hz, used fast independent component analysis (ICA) to exclude ocular artefacts by visual inspection and re-referenced to an average reference. We marked the start (T1) and end of movement (T2) manually for all trials by visual inspection of EMG data and simultaneously rejected trials with artefacts. Trials were rejected if significant EMG-activity occurred in either EMG-channel during the interval prior to movement onset. A visual judgement for significant EMG-activity was chosen to avoid automatic algorithm ambiguity and because the examiner was blinded. Trials were also rejected if visual inspection revealed movement or EMG-artefacts interfering with the EEG-channels during the trial. Out of 40 attempted trials, the participants had an average of 25.3 (SD 8.6) accepted trials from each session. We performed two parallel filtrations of the EEG data. For the main analyses of beta-ERD/ERS, we filtered the data using 2nd order IIR Butterworth filter to 13–24 Hz as used in similar investigations (23). The 24 Hz upward limit was chosen to decrease EMG contamination (24). To visually illustrate EEG dynamics in a wider frequency range, we also filtered the average reference data to 7–40 Hz for plotting of event-related spectral perturbations (ERSP). For both filtering processes, data was segmented from −4 to 4 seconds in relation to both T1 and T2 and exported. A custom-made script in MATLAB R2019b (MathWorks, USA) was used to obtain intertrial variance from the 13–24 Hz filtered data, according to Kalcher and Pfurtscheller (25), by subtracting the average at every time point, squaring and dividing by one less than the number of trials. This technique allows us to analyse only the non-phase-locked activity of ERD/ERS. For each time point, the percentage change of intertrial variance was calculated relative to a baseline −3 to −1 seconds before T1, representing beta-ERD/ERS as a percentage. Average ERD % during 0 to 2 seconds after T1 and average ERS % during 0 to 3 seconds after T2 from the C3 electrode was exported as primary variables. More negative percentage change of intertrial variance represent greater ERD. To illustrate the response between groups, beta-ERD/ERS % was plotted with a 33-width central moving average smoothing technique on the 512 Hz data (Figure 2) (11). The intervals chosen for ERD and ERS was based on blinded investigation of a similar grand mean plot of ERD/ERS % in all participants combined. The ERD interval was chosen between 0 and 2 seconds as ERD appeared to start at movement start and as the first part of the task lasted about two seconds. The ERS interval between 0 and 3 seconds was chosen to include both the gradually increasing ERS and the average peak of ERS. To also plot a time-frequency decomposition between 7 and 40 Hz illustrating the nature of the response for neighbouring frequencies, we used the EEGLAB toolbox for MATLAB (26). We performed time-frequency transform with sinusoidal wavelet increasing from three cycles at 7 Hz to 12 cycles at 40 Hz (Figure 3) (27), to obtain ERSP with comparable temporal resolution between frequencies (28) and better frequency resolution at higher frequencies (26).

Statistical analysis

We used STATA version 17.0 (StataCorp LP) for statistical analyses applying linear mixed models. Akaike and Bayesian information criteria (AIC/BIC) were evaluated between theoretically appropriated models

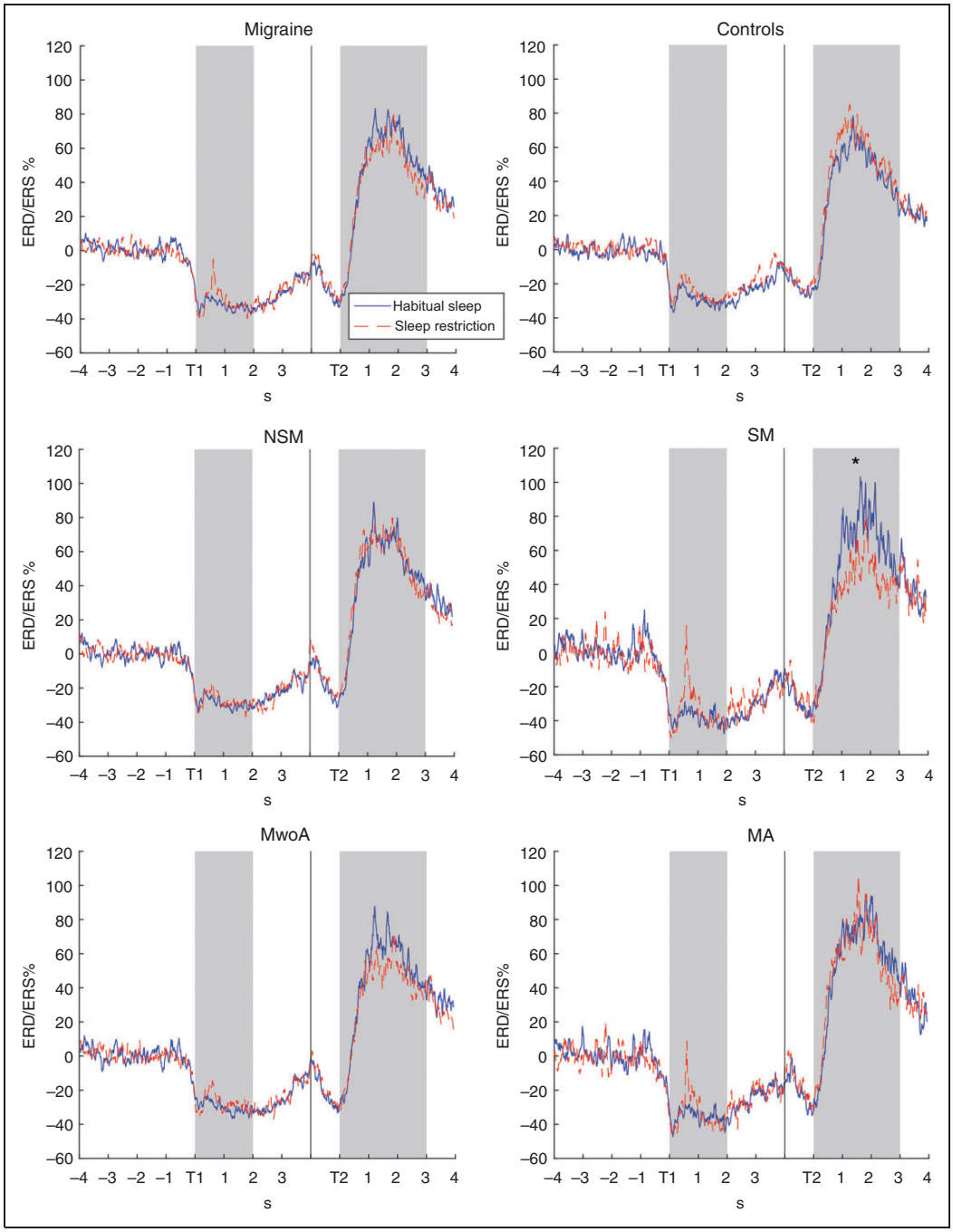

Figure 2. Beta-ERD/ERS % over time for separate groups and sleep conditions. Average beta event related desynchronisation/synchronisation % relative to the average of an individual baseline from −3 to −1 seconds (s) relative to T1, recorded from the C3 electrode. Displayed using a smoothing technique of 33-width central moving average at 512 Hz resolution. Data was filtered to

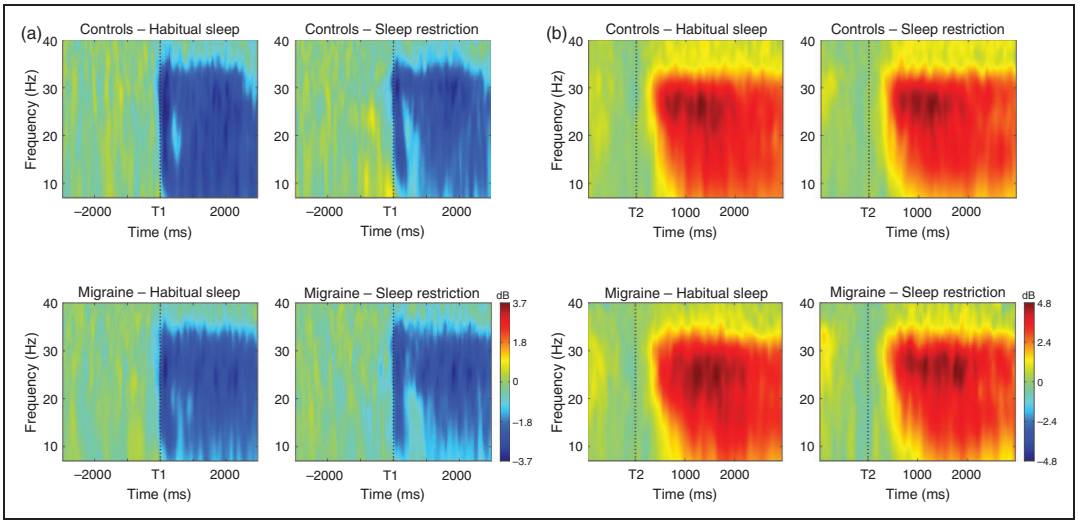

Figure 3. Event-related spectral perturbation (ERSP) between 7 and 40 Hz. Time/frequency decomposition displaying average power on a decibel scale (dB) in the frequency range 7 to 40 Hz over time, recorded from the C3 electrode. Lower negative dB values represent greater ERD, while higher positive values represent greater ERS. This figure illustrates the sensorimotor response in a larger frequency range for the main groups of interictal migraineurs and controls. Statistics were performed with linear mixed models and no significant differences were found between these groups in the primary analyses. (a) T1 represent start of movement. Blue colours represent event related desynchronisation (ERD) during the task relative to a baseline from −3000 milliseconds (ms) to −1000 ms before T1. (b) T2 represent the end of movement. Yellow and red represent event related synchronisation (ERS) following the task relative to a baseline between −500 ms and T2 (baseline used for plotting, different from baseline in analyses).

to determine the choice of model. The chosen models were 2-level random intercept models with participant ID as level 2 and sleep condition (habitual and restricted sleep), diagnosis (controls and interictal migraine) and their interaction as fixed effects. Linear mixed models are suited for handling missing data when some examinations are excluded for not being an interictal recording. Primary analyses were performed on migraine subjects and controls, and the a priori defined migraine subgroups according to headache sleep relation (NSM/SM) and presence of migraine aura (MwoA/MA). We also did post hoc analyses of the difference between migraineurs and controls after habitual sleep. For significant primary analyses, we evaluated post hoc effects of sleep restriction within the group.

To investigate the relationship between ERD/ERS and migraine phases we performed secondary analyses on the migraine group. We calculated the time in hours from the examination to the next attack and hours from the last attack to the examination and included this variable as a covariate in the model. In addition to the 68 examination of migraine subjects included the primary analyses, these analyses included an additional 11 preictal examinations (seven NSM with two habitual sleep and five sleep restriction; four SM with three habitual sleep and one sleep restriction) and seven postictal examinations (five NSM with two habitual sleep

Figure 2. Continued
13–24 Hz. The y-axis represents percentage change of intertrial variance relative to the baseline. Lower negative values represent greater ERD, while higher positive values represent greater ERS. Intertrial variance was calculated to exclude phase-locked responses. T1 represent start of movement for the self-paced hand movement with sensory discrimination task. T2 represent the end of movement. Movement was self-paced and consequently segmented separately for start and end of movement relative to T1 and T2 respectively. The solid vertical line indicates where the two different segments are merged for plotting. The first shaded area from T1 to 2 s represent the chosen interval to evaluate event related desynchronisation (ERD). The second shaded area from T2 to 3 s represent the interval chosen to evaluate event related synchronisation (ERS). The asterisk (*) represent the group and variable with significant ($p < 0.05$) interaction effects. SM displayed significantly lower beta-ERS % after sleep restriction compared to controls ($p = 0.006$) and non-sleep related migraine ($p = 0.011$). MwoA: Migraine without aura; MA: Migraine with aura; NSM: Non-sleep related migraine; SM: Sleep related migraine.

and three sleep restriction; two SM with one habitual sleep and one sleep restriction) respectively. Time to/from attack was set to 168 hours for subjects with more than a week to/from the examinations without attacks. For some examinations (n = 5) we only received headache diaries for 48 hours before/after the examination day. These examinations were excluded from the secondary analysis. The excluded examinations were four interictal from time to attack analyses (three habitual sleep, one sleep restriction) and one interictal from time from attack analyses (one sleep restriction). Two-sided p-values < 0.05 are reported as significant.

Results

Clinical and demographic data are presented in Table 1. Characteristics of the groups were similar, although usual migraine duration was numerically lower for the SM and MA group.

Migraineurs vs controls

We did not observe any difference in the effect of sleep restriction on beta-ERD % ($p = 0.98$) or beta-ERS % ($p = 0.21$) between migraineurs and controls (Table 2, Figure 4a). When analysing migraineurs and controls after habitual sleep only, we did not see any significant difference in either beta-ERD % (*contrast* $= -2.4$; *95% CI* -12.4 to 7.6; $p = 0.64$) or beta-ERS % (*contrast* $= 5.0$; *95% CI* -12.3 to 22.2; $p = 0.57$).

When we analysed the relationship between beta-ERD/ERS % and the last/next attack, we observed a greater increase in beta-ERD % and larger reduction of beta-ERS % after sleep restriction shortly after the end of the attack compared to farther from the attack end (Table 3, Figure 5a and b). This effect was seen as significant interaction effects of *sleep condition* $\times$ *time* on beta-ERD % ($p = 0.002$) and beta-ERS % ($p < 0.001$). We did not find any difference in the effect of sleep restriction over time on beta-ERD % (Table 3; $p = 0.53$) or beta-ERS % (Table 3; $p = 0.50$) before the start of an attack (Figure 5c and d).

Non-sleep related migraine (NSM) vs sleep related migraine (SM)

The SM group displayed significantly lower beta-ERS % after sleep restriction compared to controls ($p = 0.006$) and NSM ($p = 0.011$; Table 2, Figure 4b). Sleep restriction had a significant effect on beta-ERS % within the SM group alone (*contrast* $= -24.2$; *95% CI* -43.2 to -5.2; $p = 0.012$). The effect of sleep restriction on beta-ERS % was not significantly different between NSM and controls (Table 2; $p = 0.99$).

We did not find any difference in the effect of sleep restriction on beta-ERD % between SM, NSM and controls (Table 2; Figure 4b).

Migraineurs without aura (MwoA) vs migraineurs with aura (MA)

We did not see any difference between MwoA, MA and controls in effect of sleep restriction on beta-ERD % or beta-ERS % (Table 2; Figure 4c).

Discussion

The main finding of this study was lower beta-ERS during a sensorimotor task after sleep restriction in the SM group compared to both controls and NSM interictally. We did not see any interictal differences in effects of sleep restriction between migraineurs and controls or MwoA and MA. Another interesting finding was higher beta-ERD and lower beta-ERS after sleep restriction shortly after an attack compared to farther from the attack end.

Beta-ERD during movement probably represents increased firing rates of pyramidal tract neurons (29). Increased ERD during motor imagery has been associated with reduced short interval intracortical inhibition (SICI) (30). Reduced SICI has also been described after sleep restriction closely after the end of a migraine attack by our group (31). This cortical inhibitory effect is thought to mainly represent post synaptic inhibitory potentials from $\alpha 2$ or $\alpha 3$ subtype GABA-A receptor activation (32). We therefore suggest that reduced GABA-A mediated cortical inhibition may explain the increased beta-ERD we observed after sleep restriction soon after the end of an attack. Similar effects on cortical excitability due to reduced GABAergic inhibition are seen after overnight sleep deprivation in healthy subjects (33), which may indicate increased need for sufficient sleep during or closely after attacks in migraineurs.

Beta-ERS represent at least partly the inhibitory effect on cortex of somatosensory afferents (23). Increased cortical GABA concentration have been associated with increased PMBR amplitude in humans (34). Conversely, reduced PMBR has been seen with increased endogenous GABA activity due to GABA Transporter 1 blockade (35). However, blocking GABA transporters may also make a spatially confined signal into an unrestricted wave of inhibition (36), possibly explaining differences between the effect of increased spontaneous GABA concentration and transporter blockade. PMBR has also been suggested to be specifically GABA-B related (35), but this interpretation was largely based on a small study (37). Our observations of lower beta-ERS and higher beta-ERD

Table 1. Demographic and clinical data on interictal migraine subjects and controls.

	Interictal migraine *(n = 46)*	Controls *(n = 28)*	Non-sleep related migraine *(n = 32)*	Sleep related migraine *(n = 14)*	Migraine without aura *(n = 27)*	Migraine with aura *(n = 19)*
Women/men	41/5	22/6	31/1	10/4	24/3	17/2
Age (years)	37.5 (11.2)	37.5 (12.6)	35.6 (10.1)	42.0 (12.6)	37.0 (12.0)	38.3 (10.1)
Right-/left-handedness[1]	42/4	25/3	29/3	13/1	25/2	17/2
Habitual sleep/Sleep restriction[2]	35/33	28/27	24/22	11/11	19/20	16/13
Migraine usual duration (h)	21.6 (22.1)		24.5 (23.7)	15.0 (16.7)	25.2 (25.1)	16.6 (16.2)
Migraine attacks/month last 6 months (1–4)[3]	2.2 (0.4)		2.2 (0.4)	2.3 (0.5)	2.1 (0.4)	2.3 (0.5)
Migraine usual intensity (1–4)[4]	2.6 (0.5)		2.6 (0.5)	2.5 (0.5)	2.6 (0.5)	2.5 (0.5)
Headache history (years)	21.4 (11.6)		21.0 (11.8)	22.3 (11.4)	20.9 (11.4)	22.1 (12.2)
Allodynia score (0–24)[5]	4.7 (4.6)		4.6 (4.9)	5.0 (4.1)	4.4 (4.5)	5.2 (4.8)
Photophobia (0–3)[6]	2.5 (0.7)		2.7 (0.5)	2.1 (0.8)	2.4 (0.8)	2.7 (0.5)
Phonophobia (0–3)[6]	2.2 (0.9)		2.4 (0.8)	1.6 (0.7)	2.2 (0.9)	2.2 (0.8)
Osmophobia (0–3)[6]	1.6 (1.2)		1.8 (1.2)	1.1 (1.2)	1.4 (1.3)	1.8 (1.1)
Sleep time (habitual) (min)[7]	452.9 (35.8)	459.7 (28.2)	455.2 (32.4)	448.0 (43.6)	459.1 (32.6)	445.5 (39.0)
Sleep time (restricted) (min)[7]	258.8 (41.5)	247.4 (23.4)	256.2 (38.6)	263.9 (48.3)	260.7 (41.7)	255.8 (42.6)

The table display data as mean (SD) or number of participants. Migraine subjects had at least one recording in the interictal phase.
[1]Self reported preferential use of one hand.
[2]Number of examinations following either habitual sleep or restricted sleep nights.
[3]Categories: 1 = less than 1 per month, 2 = 1–3 per month, 3 = 4–5 per month, 4 = 6 or more per month.
[4]Categories: 1 = light – can keep doing a task, 2 = moderate – can do light tasks, 3 = strong – must lie down, 4 = extremely strong – cannot lay still.
[5]Allodynia score (ASC-12) during usual migraine attacks.
[6]Symptom in migraine attacks when not medically treated: 0 = no symptom, 1 = to a small degree, 2 = to a medium degree, 3 = to a strong degree.
[7]Mean sleep time for the two sleep-controlled nights for each sleep condition from actigraphy recording.

Table 2. Interaction effects of sleep and group on beta-ERD % and beta-ERS % at electrode C3.

	Beta-ERD/ERS %				
	z-statistic	p-value	coefficient	95 % CI	
ERD					
Migraine/Controls	−0.02	0.98	−0.7	−6.6	6.4
NSM/Controls	0.53	0.60	1.9	−5.3	9.2
SM/Controls	−0.80	0.42	−3.7	−12.6	5.3
SM/NSM	−1.13	0.26	−5.6	−15.3	4.1
MwoA/Controls	−0.22	0.83	−0.9	−8.6	6.9
MA/Controls	0.15	0.88	0.7	−7.7	9.0
MA/MwoA	0.31	0.76	1.5	−8.0	11.0
ERS					
Migraine/Controls	−1.26	0.21	−10.7	−27.2	5.9
NSM/Controls	−0.01	0.99	−0.1	−17.7	17.5
SM/Controls	−2.75	**0.006***	−30.7	−52.7	−8.8
SM/NSM	−2.56	**0.01***	−30.6	−54.1	−7.15
MwoA/Controls	−1.08	0.28	−10.8	−30.3	8.7
MA/Controls	−0.88	0.38	−9.5	−30.7	11.7
MA/MwoA	0.11	0.92	1.3	−22.4	24.9

ERD, Event-related desynchronization; ERS, Event-related synchronization; NSM, Non-sleep related migraine; SM, Sleep related migraine; MwoA, Migraine without aura; MA, Migraine with aura. Results from the interaction *habitual sleep/restricted sleep* × *group* in 2-level random intercept models, including z-test statistic, p-value, the coefficient and 95% confidence intervals (CI) for beta-ERD/ERS % difference between groups and sleep conditions. ERD was averaged during 0–2 s after start of movement (T1) and ERS was averaged during 0–3 seconds after end of movement (T2). Both measures were recorded from electrode C3 during a sensorimotor task with the right hand and calculated relative to the baseline −3 to −1 second before T1. The asterisk (*) and bold text indicate $p < 0.05$.

Table 3. Interaction effects of sleep and temporal relation to migraine attacks on beta-ERD % and beta-ERS %.

	n	z-statistic	p-value	Beta-ERD/ERS % coefficient	95 % CI	
Time from attack to examination (h)						
ERD	48	3.12	**0.002***	0.15	0.06	0.24
ERS	48	3.60	**<0.001***	0.46	0.21	0.71
Time from examination to attack (h)						
ERD	46	0.62	0.53	0.03	0.06	0.11
ERS	46	0.68	0.50	0.07	−0.13	0.27

Results from the interaction *habitual sleep/restricted sleep* × *time to/from examination from/to attack* in 2-level random intercept models, including number of subjects (n), z-test statistic, p-value, the coefficient and 95% confidence intervals (CI) for beta-ERD/ERS % difference between sleep conditions per time point (h). ERD was averaged during 0–2 s after start of movement and ERS was averaged during 0–3 seconds after end of movement. Both measures were recorded from electrode C3 during a sensorimotor task with the right hand. ERD, Event-related desynchronization; ERS, Event-related synchronization. The asterisk (*) and bold text indicate $p < 0.05$.

after sleep restriction soon after the end of an attack may be caused by alterations of GABA concentration, GABA receptor activity or receptor expression related to an increased need for sufficient sleep.

The reduction in beta-ERS we observed in the SM group following sleep restriction may be caused by GABAergic inhibitory effects on cortex from somatosensory afferents (37). Our group has previously identified SM to have an increased number of awakenings and less stage 3 slow-wave sleep than NSM, indicating a preserved or hyperactive arousal system (17). Both GABA-B receptor activity and GABA-A activation appear to increase slow-wave sleep and decrease waking (38). Consequently, an underlying GABAergic dysfunction causing disturbed sleep may be involved in SM, becoming further dysregulated with sleep restriction. However, possible GABA-B mediated effects in SM is likely different from the altered function of dopamine regulated GABA-B inhibitory duration we previously observed after sleep restriction in NSM, but not in SM (18). Furthermore, preventive medication increasing GABA levels such as valproate and gabapentin, are used in migraineurs with varying effect (39). The SM and NSM subgroups of migraine

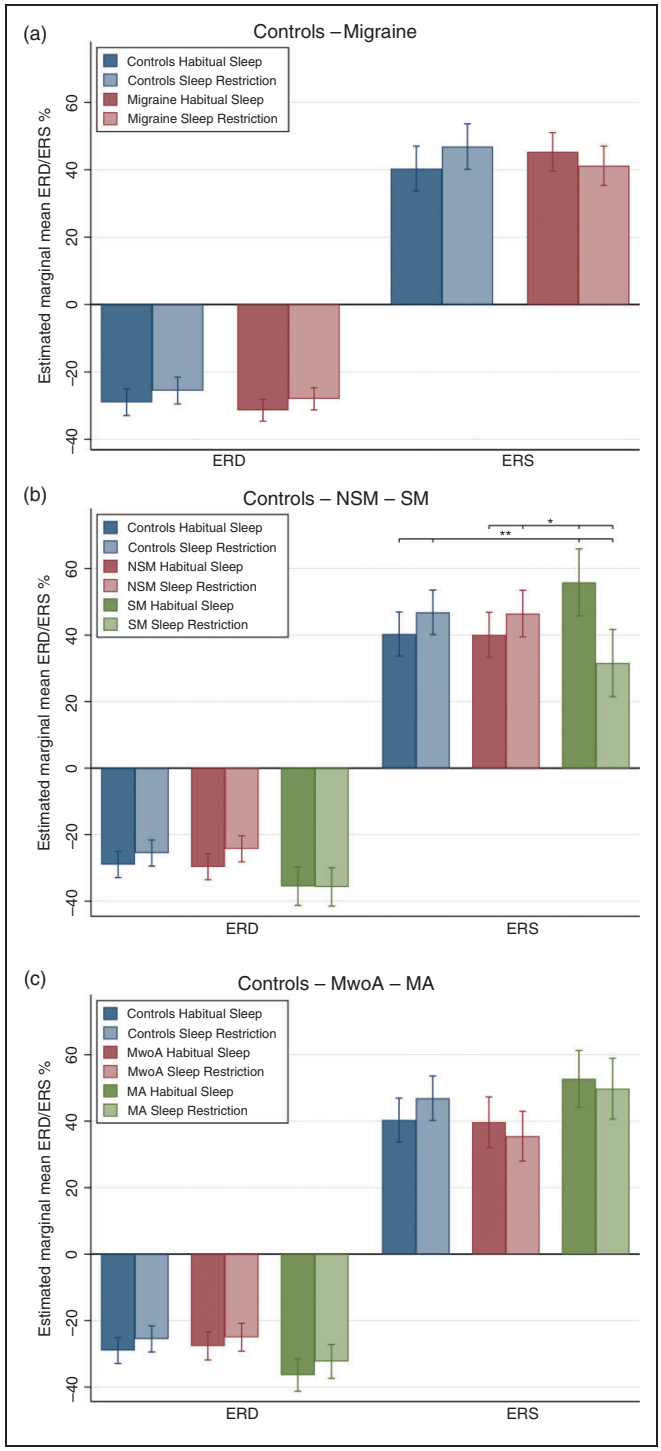

Figure 4. Estimated marginal mean beta-ERD/ERS % for separate groups and sleep conditions. Bar plots representing estimated marginal mean beta event related desynchronisation/synchronisation (ERD/ERS) % for frequencies between 13 and 24 Hz relative to

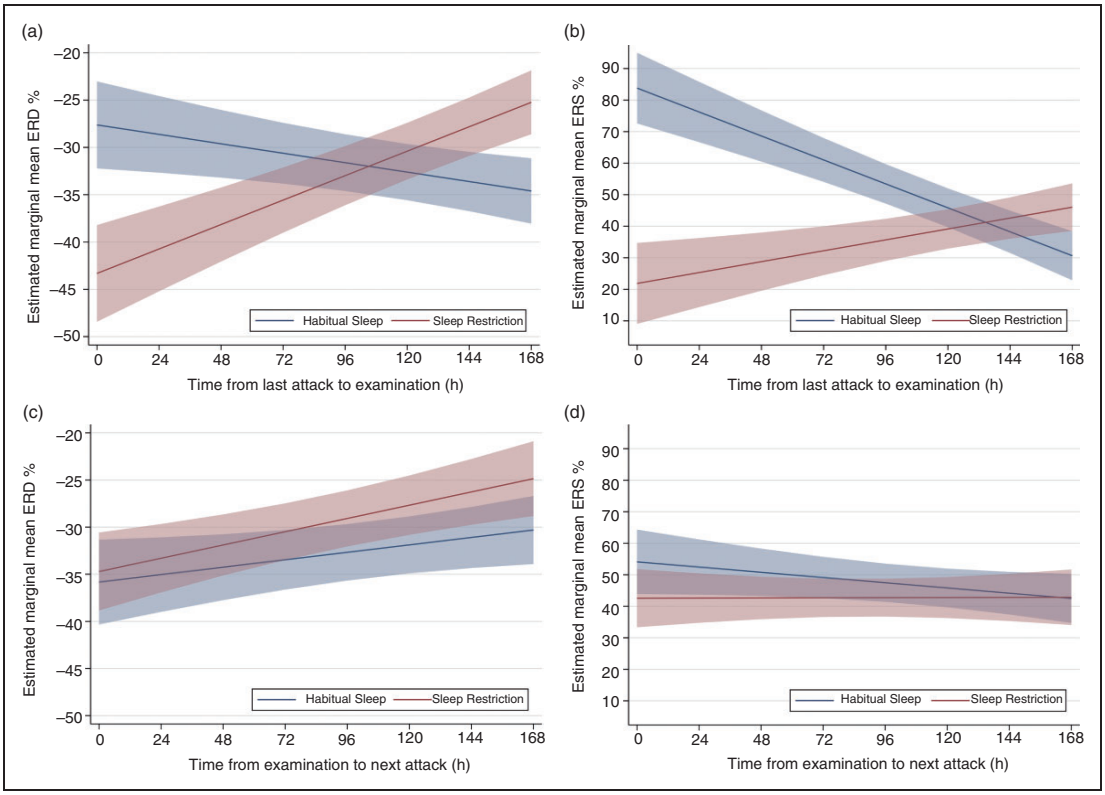

Figure 5. Estimated marginal mean ERD/ERS % for interictal migraineurs in temporal relation to an attack. Line plots representing estimated marginal mean beta event related desynchronisation/synchronisation (ERD/ERS) % over time (h) in relation to the last/next migraine attack for frequencies between 13 and 24 Hz relative to a pre-movement baseline. Lower negative values represent greater ERD, while higher positive values represent greater ERS. Marginal means are estimated from linear mixed models of migraineurs including time relative to the last/next migraine attack, sleep condition and their interaction and are reported separately for recordings after habitual sleep and sleep restriction. The shaded area indicates estimated marginal standard error. (a) and (b) display results from models with significant interaction effects of *time from last attack to examination* × *sleep condition* for ERD ($p = 0.002$) and ERS ($p < 0.001$) respectively. (c) and (d) display results from models with non-significant interaction effects of *time from examination to next attack* × *sleep condition* for ERD ($p = 0.53$) and ERS ($p = 0.50$) respectively.

may therefore be susceptible to sleep restriction induced effects on different parts of GABAergic inhibitory systems. There is a possibility that this differentiation may account for differences in responses to preventive medication.

Neurophysiological characteristics are thought to be similar in MA and MwoA. We observed some indications of different effects of sleep restriction on GABAergic systems between these subgroups in a previous study, but the pattern of effects was not definite (18). The findings in the present study do not support that insufficient sleep affect sensorimotor processing differently in MwoA and MA. Neither did we observe any effects which differed between migraineurs in

Figure 4. Continued
a pre-movement baseline. Lower negative values represent greater ERD, while higher positive values represent greater ERS. Marginal means are estimated from linear mixed models and reported separately for recordings after habitual sleep and sleep restriction. Asterisks indicate significant effects of the interaction *group* × *sleep condition* at levels $p < 0.05$ (*) and $p < 0.01$ (**). Capped spikes indicate estimated marginal standard error. (a) Results from a linear mixed model including healthy controls and interictal migraineurs. (b) Results from a model including controls, non-sleep related migraine (NSM) and sleep related migraine (SM). (c) Results from a model with controls, migraine without aura (MwoA) and migraine with aura (MA).

general and controls. This lack of differences may be a consequence of heterogeneity within the migraine diagnosis and differences between the pathophysiology of migraine subgroups (10).

Strengths and limitations

A strength of this study is the randomised, blinded crossover design.

We chose 24 hours from the start and end of migraine headache as the cut off for defining the interictal phase in this study. However, the possible gradual evolvement, length and variation of the migraine phases are currently unknown and some authors suggest that the preictal phase may last up to 48 hours before the start of headache (40). There is a possibility that distinct phasic properties of individual migraineurs overlap between the defined phases in the study.

Migraine subjects did not fill in a headache diary prior to recruitment. This allows for theoretical uncertainty of exact headache characteristics in the period leading up to the study. However, every subject was evaluated for inclusion by a neurologist with experience in headache according to ICHD-3 criteria.

We did not correct for multiple analyses in this study to not assume all null hypotheses to be simultaneously true (41). To be able to conduct subgroup analyses, we recruited a larger migraine group. Analyses of the smaller subgroups have lower power which should be recognised when interpreting the results.

EMG contamination is an important limiting factor of scalp EEG above 20 Hz frequencies. Contamination is described to be least in central electrodes. Here, muscle activity contributes to a 1 to 6-fold power increase in frequencies between 25–30 Hz. Consequently, we chose an upper limit for the beta band of 24 Hz to limit EMG contamination at the C3 electrode (24).

Conclusion

The findings suggest that GABAergic inhibitory systems may be dysfunctional in the sleep related subgroup of migraineurs. Furthermore, the findings suggest that migraineurs have an increased need for sufficient sleep during or closely after attacks, possibly to maintain cortical GABAergic function.

Article highlights

- The GABAergic system in individuals that usually have migraine attacks during sleep may be dysfunctional.
- Migraineurs are more susceptible to changes in cortical GABAergic functioning and sensorimotor processing due to insufficient sleep during or close after the end of an attack.
- Migraineurs with predominantly sleep related attacks may be an important migraine subgroup.

Ethics approval and consent to participate

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was approved by the Regional Committee for Medical Research Ethics Central Norway. Written, informed consent was obtained from all participants.

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Authors' contributions

All the authors have read and approved the final version of the manuscript. MSM, MU, TS and PMO designed and planned the study. MSM conducted the examinations, performed data analyses and statistical analyses, and drafted the first version of the manuscript. MU, MHB, DM, TS and PMO contributed to the process of data analysis and made important contributions to the manuscript.

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