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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

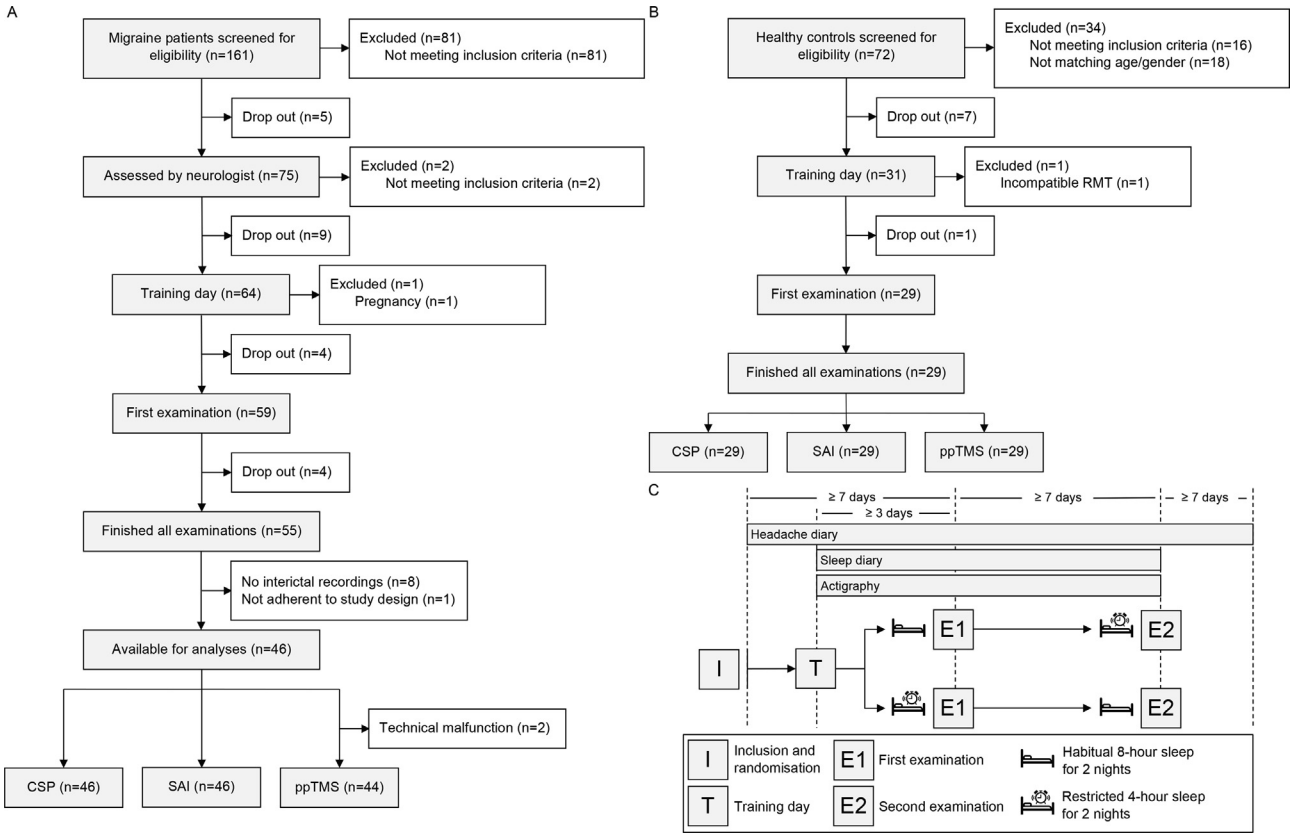

Fig. 1. Study design and inclusion. Flow chart for the participant inclusion process for (**A**) migraine subjects and (**B**) healthy controls, reporting number of participants (n) for each step. (**C**) Overview of the study design which was equal for migraine subjects and controls. Participants were 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-

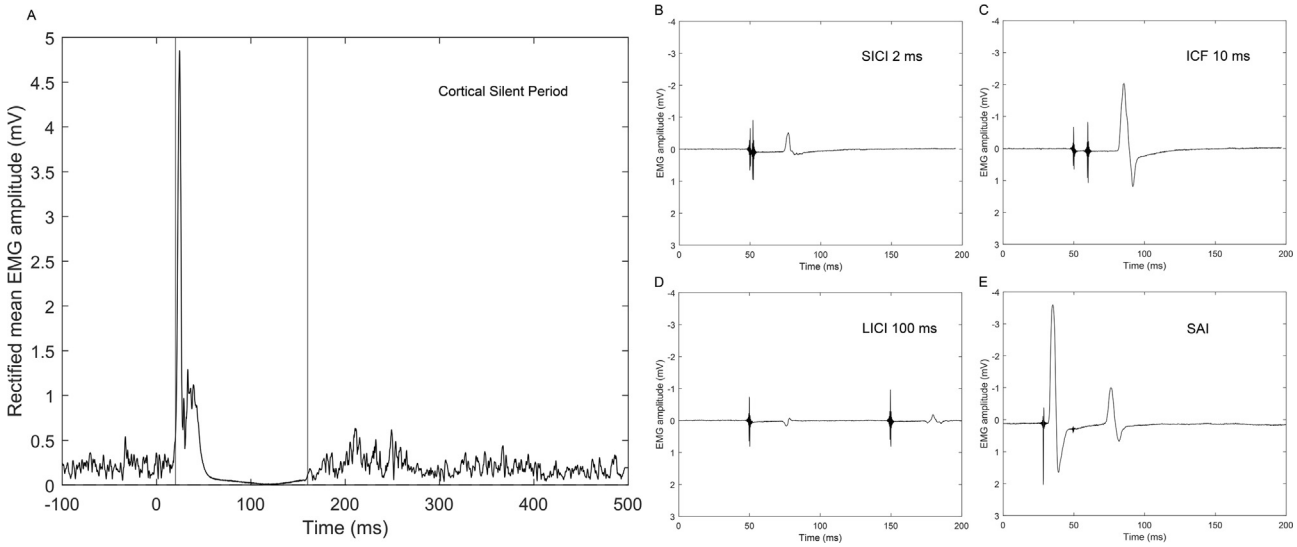

Fig. 2. Cortical silent period and paired pulse TMS illustrations. (**A**) Rectified mean electromyography (EMG) amplitude in millivolts (mV) during time in milliseconds (ms) for one session of Cortical silent period (CSP) recording for a single participant. EMG was recorded from the abductor pollicis 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

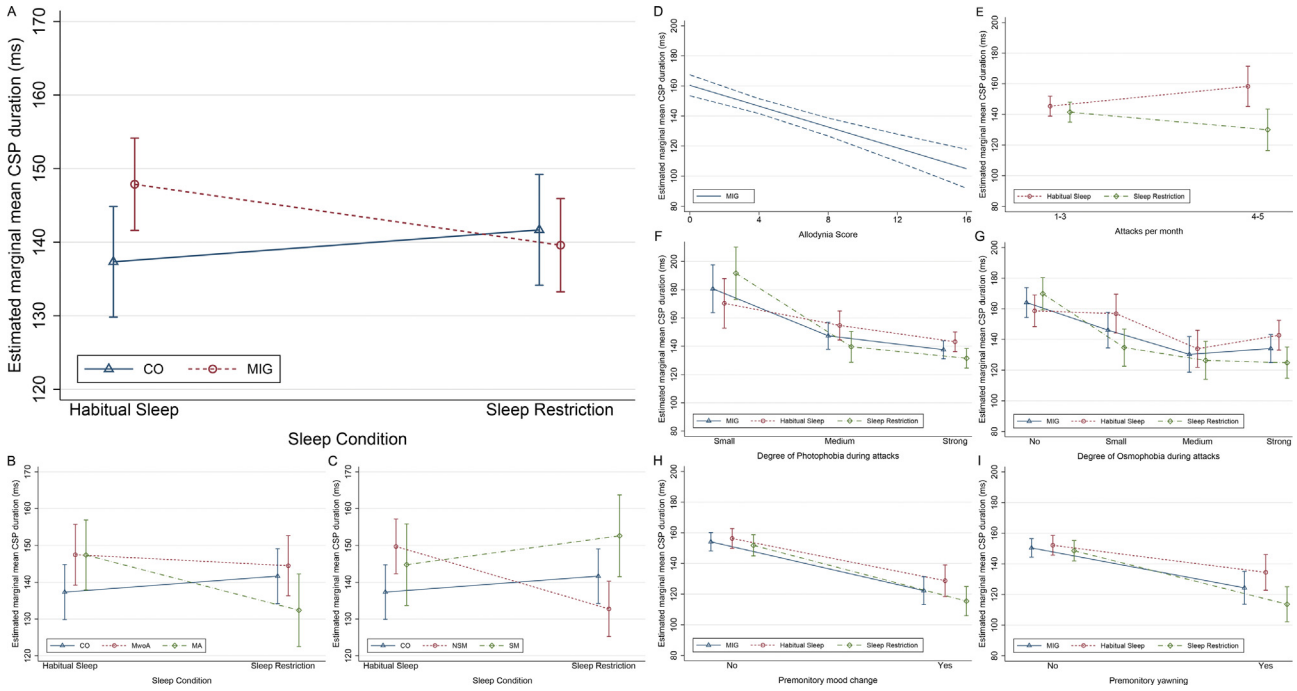

Fig. 3. Estimated marginal means of cortical silent period (CSP) duration. (**A, B, C**) Estimated marginal means of cortical silent period (CSP) duration in milliseconds (ms) from random intercept models of interaction with diagnosis and sleep condition in interictal migraine and controls. (**A**) Blue 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)

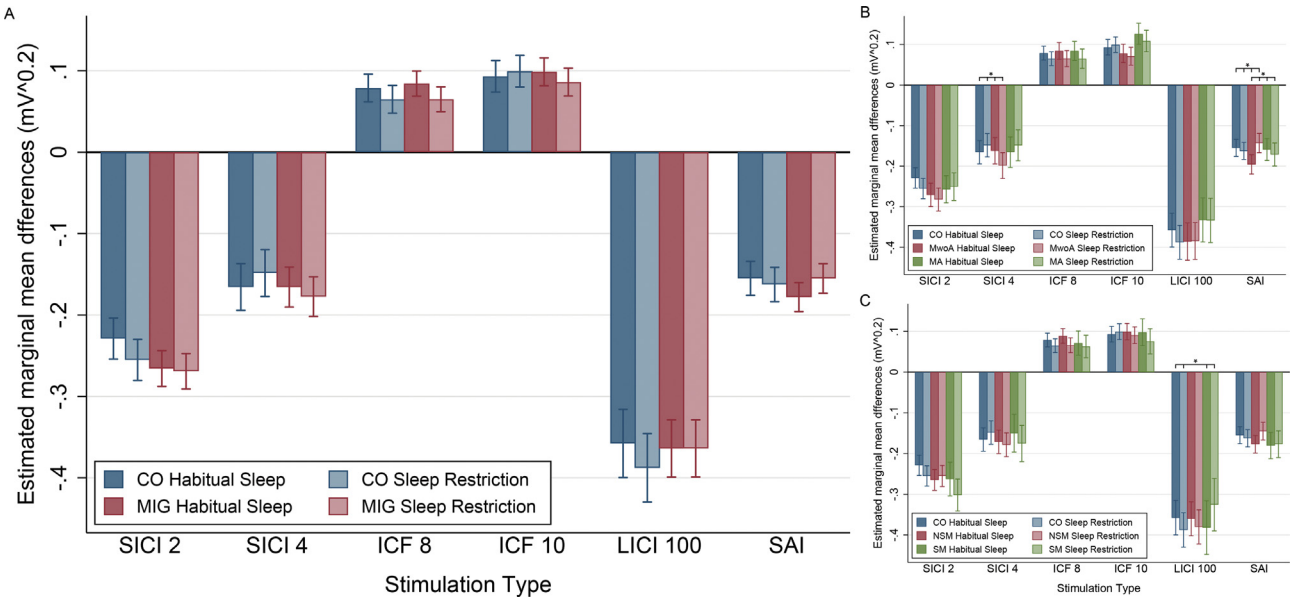

Fig. 4. Estimated marginal means of paired pulse transcranial magnetic stimulation (ppTMS) and short-latency afferent inhibition. Figures display estimated marginal mean motor evoked potential (MEP) amplitude differences in millivolts to the power of 0.2 ($mV^{0.2}$) between each paired pulse type and 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 $\alpha 2$ and $\alpha 3$ 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 $\alpha 1$ 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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