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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

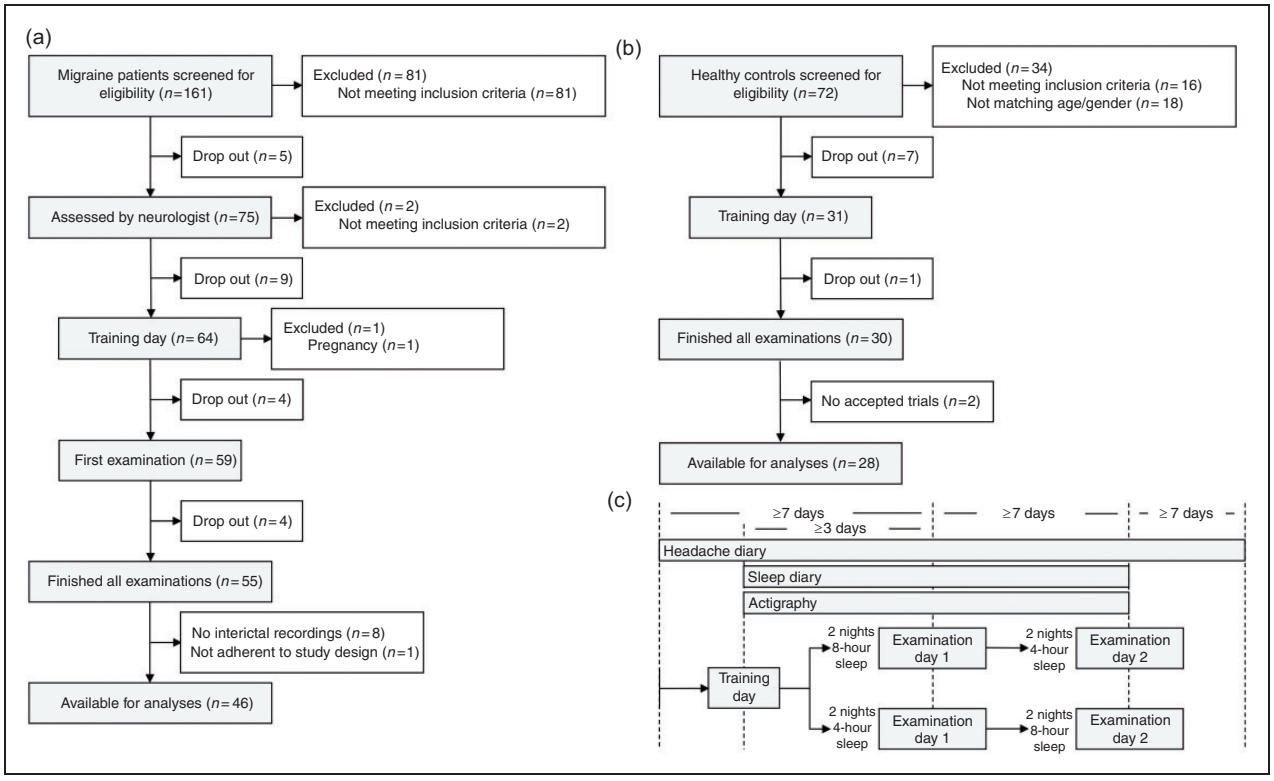

Figure 1. Inclusion and exclusion flow chart and study design, (a) and (b) show flow chart for the process of inclusion and exclusion, reporting number of participants (n) at every stage and (c) Study design chart depicting how every participant underwent one training day followed by two examination 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 prerehearsed 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

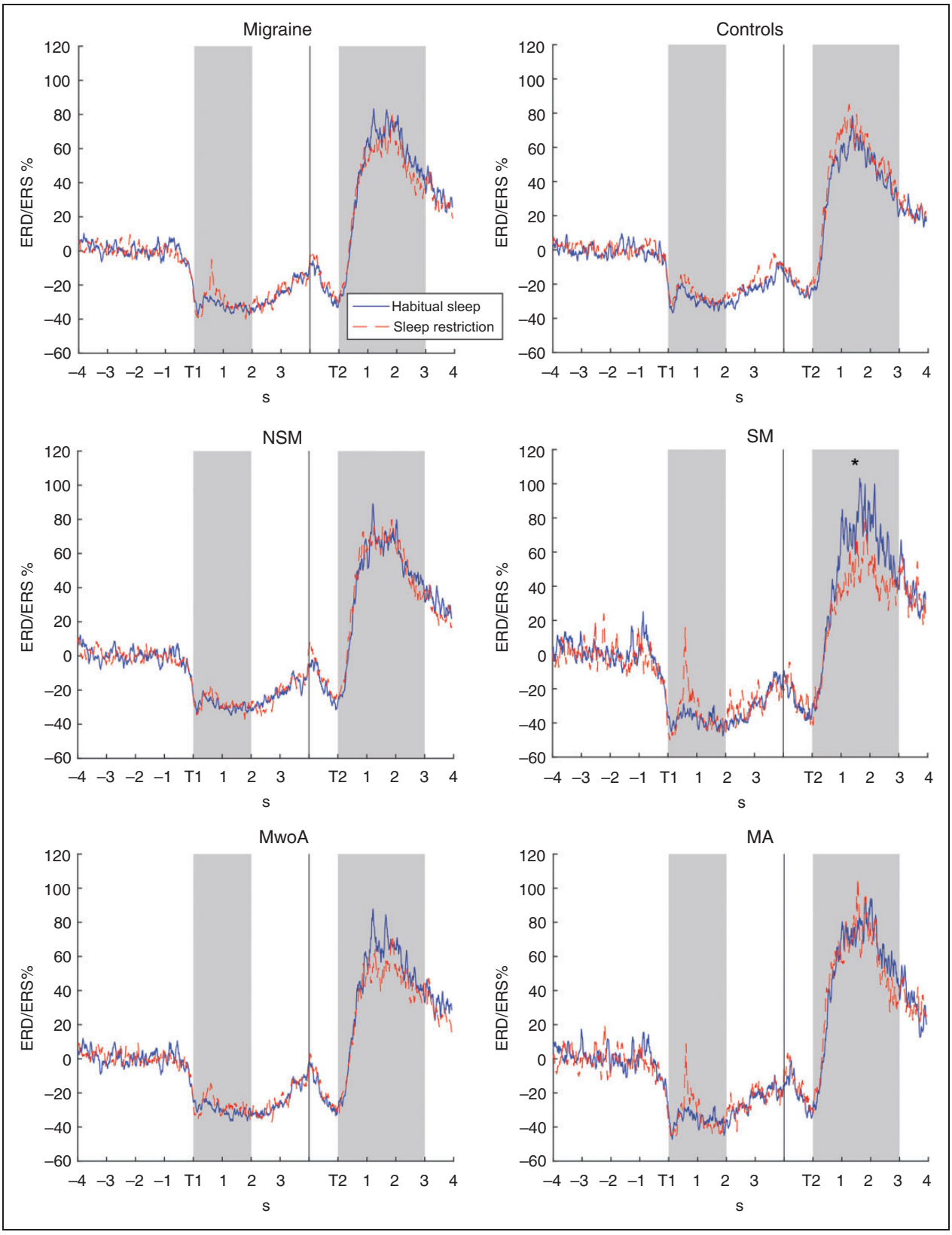

Figure 2. Beta-ERD/ERS % over time for separate groups and sleep conditions. Average beta event related desynchronisation/synchronisation % relative to the average of an individual baseline from −3 to −1 seconds (s) relative to T1, recorded from the C3 electrode. Displayed using a smoothing technique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

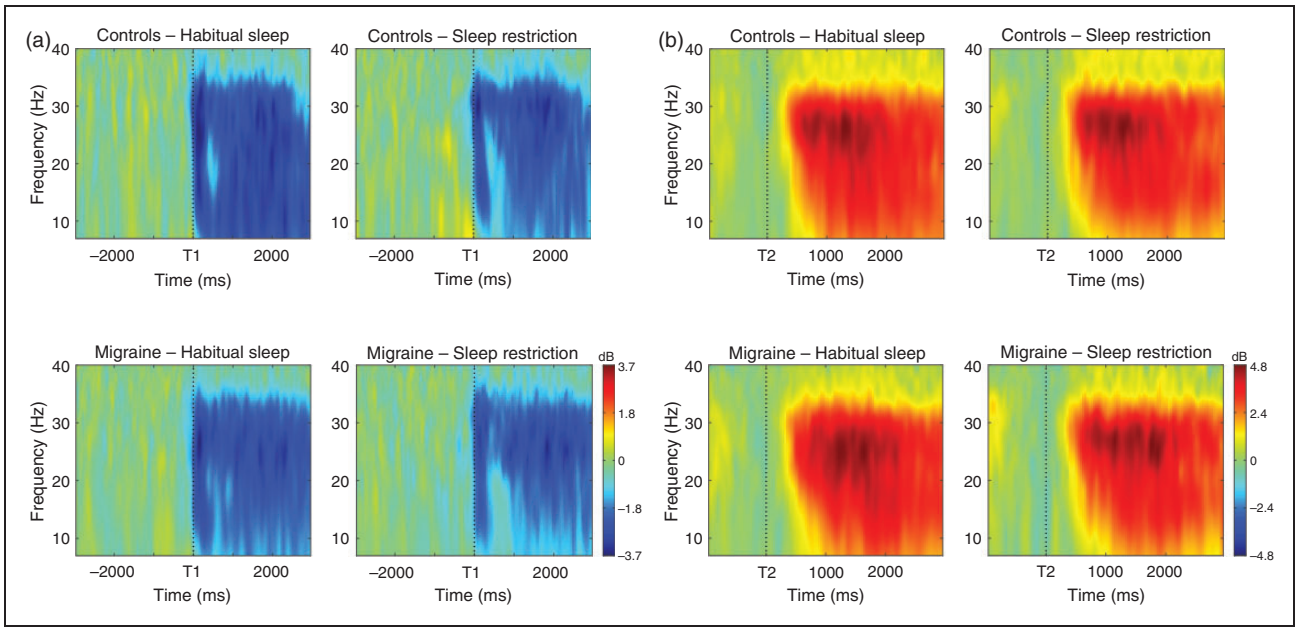

Figure 3. Event-related spectral perturbation (ERSP) between 7 and 40 Hz. Time/frequency decomposition displaying average power on a decibel scale (dB) in the frequency range 7 to 40 Hz over time, recorded from the C3 electrode. Lower negative dB values represent greater ERD, while higher positive values 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* × *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 α2 or α3 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

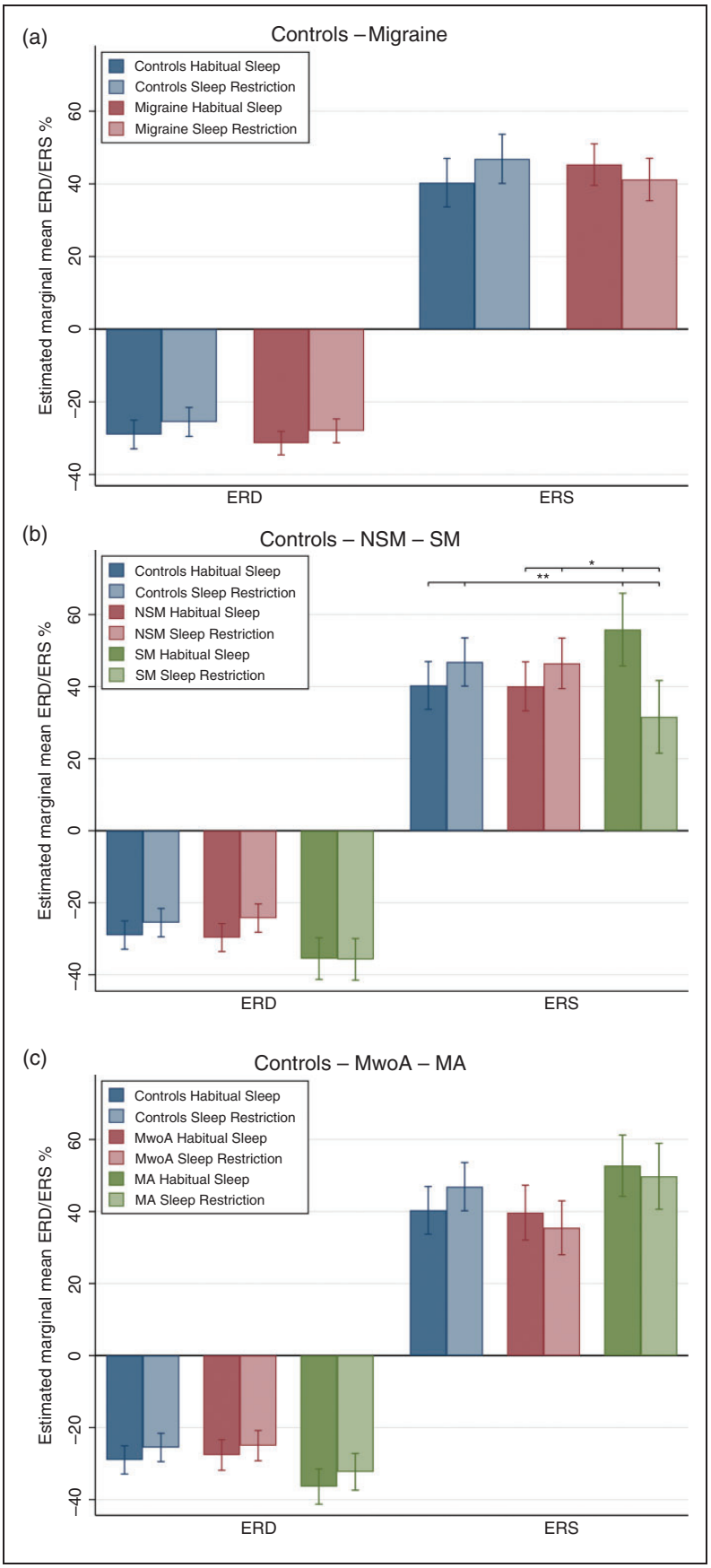

Figure 4. Estimated marginal mean beta-ERD/ERS % for separate groups and sleep conditions. Bar plots representing estimated marginal mean beta event related desynchronisation/synchronisation (ERD/ERS) % for frequencies between 13 and 24 Hz relative to

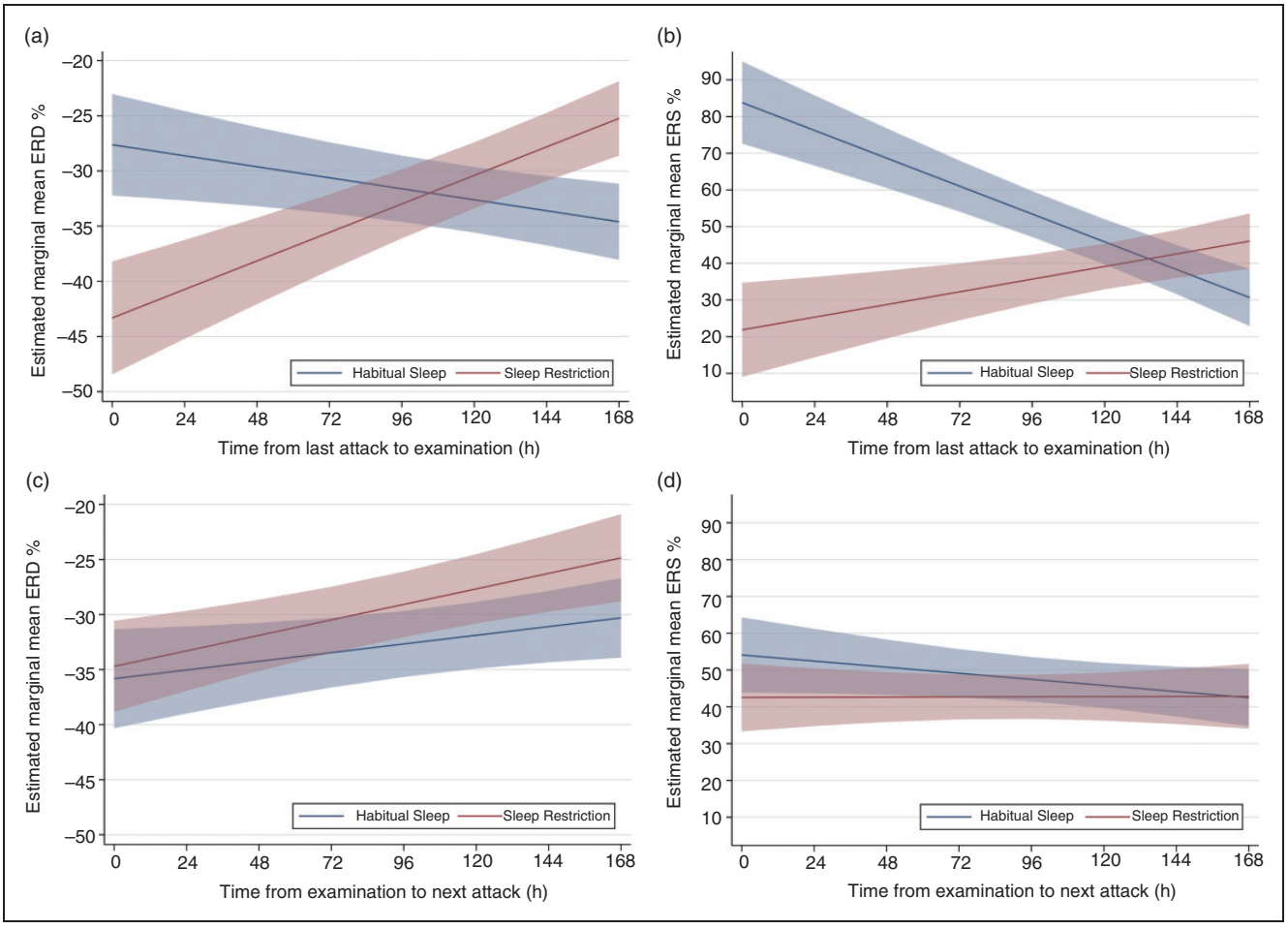

Figure 5. Estimated marginal mean ERD/ERS % for interictal migraineurs in temporal relation to an attack. Line plots representing estimated marginal mean beta event related desynchronisation/synchronisation (ERD/ERS) % over time (h) in relation to the last/next migraine attack for frequencies between 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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References

1. Kelman L and Rains JC. Headache and sleep: examination of sleep patterns and complaints in a large clinical sample of migraineurs. *Headache* 2005; 45: 904–910.
2. Vgontzas A and Pavlovic JM. Sleep disorders and migraine: review of literature and potential pathophysiology mechanisms. *Headache* 2018; 58: 1030–1039.
3. Blau JN. Resolution of migraine attacks: sleep and the recovery phase. *J Neurol Neurosurg Psychiatry* 1982; 45: 223–226.
4. Vgontzas A, Li W, Mostofsky E, et al. Baseline sleep quality, stress, and depressive symptoms, and subsequent headache occurrence in a six-week prospective cohort study of patients with episodic migraine. *Headache* 2021; 61: 727–733.
5. de Tommaso M, Delussi M, Vecchio E, et al. Sleep features and central sensitization symptoms in primary headache patients. *J Headache Pain* 2014; 15: 64.
6. Coppola G, Bracaglia M, Di Lenola D, et al. Lateral inhibition in the somatosensory cortex during and between migraine without aura attacks: Correlations with thalamocortical activity and clinical features. *Cephalalgia* 2016; 36: 568–578.
7. Curra A, Pierelli F, Coppola G, et al. Shortened cortical silent period in facial muscles of patients with migraine. *Pain* 2007; 132: 124–131.
8. Cosentino G, Brighina F, Talamanca S, et al. Reduced threshold for inhibitory homeostatic responses in migraine motor cortex? A tDCS/TMS study. *Headache* 2014; 54: 663–674.
9. Tu Y, Fu Z, Zeng F, et al. Abnormal thalamocortical network dynamics in migraine. *Neurology* 2019; 92: e2706–e2716.
10. Cosentino G, Fierro B and Brighina F. From different neurophysiological methods to conflicting pathophysiological views in migraine: a critical review of literature. *Clin Neurophysiol* 2014; 125: 1721–1730.
11. Pfurtscheller G and Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clin Neurophysiol* 1999; 110: 1842–1857.
12. Mykland MS, Bjork MH, Stjern M, et al. Fluctuations of sensorimotor processing in migraine: a controlled longitudinal study of beta event related desynchronization. *J Headache Pain* 2019; 20: 77.
13. Nakayashiki K, Saeki M, Takata Y, et al. Modulation of event-related desynchronization during kinematic and kinetic hand movements. *J Neuroeng Rehabil* 2014; 11: 90.
14. Houdayer E, Labyt E, Cassim F, et al. Relationship between event-related beta synchronization and afferent inputs: analysis of finger movement and peripheral nerve stimulations. *Clin Neurophysiol* 2006; 117: 628–636.
15. Barone J and Rossiter HE. Understanding the role of sensorimotor beta oscillations. *Front Syst Neurosci* 2021; 15: 655886.
16. Mykland MS, Bjork MH, Stjern M, et al. Alterations in post-movement beta event related synchronization throughout the migraine cycle: A controlled, longitudinal study. *Cephalalgia* 2018; 38: 718–729.
17. Engstrom M, Hagen K, Bjork MH, et al. Sleep quality and arousal in migraine and tension-type headache: the headache-sleep study. *Acta Neurol Scand Suppl* 2014: 47–54.
18. Mykland MS, Uglem M, Neverdahl JP, et al. Sleep restriction alters cortical inhibition in migraine: A transcranial magnetic stimulation study. *Clin Neurophysiol* 2022; 139: 28–42.
19. Lateef T, Swanson S, Cui L, et al. Headaches and sleep problems among adults in the United States: findings from the National Comorbidity Survey-Replication study. *Cephalalgia* 2011; 31: 648–653.
20. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38: 1–211.
21. Neverdahl JP, Uglem M, Matre D, et al. Pain thresholds and suprathreshold pain after sleep restriction in migraine – A blinded crossover study. *Cephalalgia* 2022; 42: 466–480.
22. Chatrian GE, Lettich E and Nelson PL. Ten Percent Electrode System for Topographic Studies of Spontaneous and Evoked EEG Activities. *Am J EEG Technol* 1985; 25: 83–92.
23. Cassim F, Monaca C, Szurhaj W, et al. Does post-movement beta synchronization reflect an idling motor cortex? *Neuroreport* 2001; 12: 3859–3863.
24. Whitham EM, Pope KJ, Fitzgibbon SP, et al. Scalp electrical recording during paralysis: quantitative evidence that EEG frequencies above 20 Hz are contaminated by EMG. *Clin Neurophysiol* 2007; 118: 1877–1888.
25. Kalcher J and Pfurtscheller G. Discrimination between phase-locked and non-phase-locked event-related EEG activity. *Electroencephalogr Clin Neurophysiol* 1995; 94: 381–384.
26. Delorme A and Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods* 2004; 134: 9–21.
27. Bocharov AV, Savostyanov AN, Tamozhnikov SS, et al. Oscillatory dynamics of perception of emotional sentences in healthy subjects with different severity of depressive symptoms. *Neurosci Lett* 2020; 728: 134888.
28. Rossi A, Parada FJ, Kolchinsky A, et al. Neural correlates of apparent motion perception of impoverished facial stimuli: a comparison of ERP and ERSP activity. *Neuroimage* 2014; 98: 442–459.
29. van Wijk BC, Beek PJ and Daffertshofer A. Neural synchrony within the motor system: what have we learned so far? *Front Hum Neurosci* 2012; 6: 252.
30. Takemi M, Masakado Y, Liu M, et al. Event-related desynchronization reflects downregulation of intracortical inhibition in human primary motor cortex. *J Neurophysiol* 2013; 110: 1158–1166.
31. Mykland MS, Uglem M, Stovner LJ, et al. Insufficient sleep may alter cortical excitability near the migraine

attack: A blinded TMS crossover study [Manuscript submitted for publication]. Norwegian University of Science and Technology, 2022.
32. Ziemann U, Reis J, Schwenkreis P, et al. TMS and drugs revisited 2014. *Clin Neurophysiol* 2015; 126: 1847–1868.
33. Salehinejad MA, Ghanavati E, Reinders J, et al. Sleep-dependent upscaled excitability, saturated neuroplasticity, and modulated cognition in the human brain. *Elife* 2022; 11: e69308.
34. Gaetz W, Edgar JC, Wang DJ, et al. Relating MEG measured motor cortical oscillations to resting gamma-aminobutyric acid (GABA) concentration. *Neuroimage* 2011; 55: 616–621.
35. Muthukumaraswamy SD, Myers JF, Wilson SJ, et al. The effects of elevated endogenous GABA levels on movement-related network oscillations. *Neuroimage* 2013; 66: 36–41.
36. Scimemi A. Structure, function, and plasticity of GABA transporters. *Front Cell Neurosci* 2014; 8: 161.
37. Hall SD, Stanford IM, Yamawaki N, et al. The role of GABAergic modulation in motor function related neuronal network activity. *Neuroimage* 2011; 56: 1506–1510.
38. Gottesmann C. GABA mechanisms and sleep. *Neuroscience* 2002; 111: 231–239.
39. D'Andrea G, Granella F, Cataldini M, et al. GABA and glutamate in migraine. *J Headache Pain* 2001; 2: s57–s60.
40. Peng KP and May A. Redefining migraine phases – a suggestion based on clinical, physiological, and functional imaging evidence. *Cephalalgia* 2020; 40: 866–870.
41. Perneger TV. What's wrong with Bonferroni adjustments. *BMJ* 1998; 316: 1236–1238.