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Alterations in post-movement beta event related synchronization in relation to migraine attacks; a controlled, longitudinal study

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Summary

Background: The migraine brain is believed to have altered excitability compared to controls and between migraine cycle phases. Our aim was to evaluate excitability through post-movement beta event related synchronization (PMBS) in sensorimotor cortices with and without sensory discrimination.

Subjects and methods: We recorded EEG of 41 migraine patients and 33 age and sex matched healthy controls on three different days with classification of days in relation to migraine pain attack phases (interictal, preictal < 36 h before attack, ictal and postictal <36 h after attack). During each recording, subjects performed one motor test with flexion and extension of the right wrist as well as a sensorimotor task (with a sensory assessment in addition to the motor task). Controls and migraine patients in the interictal phase were compared with repeated measures (R-) ANOVA and two sample Student's t-test. Migraine phases were compared to the interictal phase with R-ANOVA and paired Student's t-test.

Results: R-ANOVA results suggested that migraine patients had reduced difference between PMBS at contralateral (C3) and ipsilateral (C4) sensorimotor cortex in the preictal phase compared to the interictal phase and increased difference between PMBS at contralateral (C3) and ipsilateral (C4) sensorimotor cortex in the ictal phase compared to the interictal phase. Paired t-test showed that changes specifically occurred for ipsilateral right cortex (C4) after the sensorimotor task with significantly decreased PMBS ictally compared to the interictal phase and a tendency towards increased PMBS preictally compared to the interictal phase. No differences between migraine patients and controls were seen in the interictal phase.

Conclusion: The cyclic changes in PMBS for migraine patients may indicate that a dysfunction in sensorimotor cortex is involved in the migraine attack cascade. Current understanding of the PMBS phenomenon suggests that it is the level of cortical inhibition that is subject to cyclic modulation. This modulation, regulating the overall cortical excitability, may play a role in migraine attack initiation and continuation Elevated ipsilateral PMBS levels preictally and lowered ipsilateral PMBS ictally may consequently represent asymmetric cyclic changes, from somatosensory hypo- to hyperexcitability, as a result of alterations in basic cortical inhibitory mechanisms.

Introduction

About 13 % of adults are affected by migraine (1).The disorder has extensive impact on working abilities and social capacity for the individual (2, 3) as well as significant economic consequences for society (4). Migraine pain attacks last for 4 to 72 hours with interictal periods of varying length. Each attack has a premonitory (preictal) and postictal phase; often defined as the time periods 24-72 hours before and after the migraine attack. Neurophysiological changes have been found in these intervals compared to the interictal phase and compared to healthy controls. Understanding how the neurophysiology changes between these cyclic phases may constitute an opportunity for applying new therapeutic strategies (5). However, the neurophysiology of the migraine cycle has not been clarified and this matter needs further investigation with longitudinal studies.

Electrophysiological investigation of migraine neurophysiology have shown different and partly contradicting results (6). At first, it was believed that the migraine cortex responded excessively to stimuli, being generally hyperexcitable; however, later studies found contradicting results regarding cortical excitability in migraine, suggesting both a cortical hypo- and hyperexcitability (6-10). Several studies with different neurophysiological modalities suggest that defective habituation[1] to sensory stimuli may be the underlying mechanism. However this "neurophysiological hallmark" is somewhat controversial as recent, blinded studies have failed to reproduce the results (12, 13). Different theories have been suggested to unify the findings. The "ceiling theory" suggests reduced pre-activation excitability in migraine interictally, leading to a wider range of suprathreshold activation ("potentiation") before the "ceiling" is reached and habituation may occur with further stimulation (14, 15). Furthermore other findings suggest an increase in thalamocortical activation before and during the migraine pain attack implying that cortical pre-activation levels normalize in the ictal phase (15).

[1] Habituation is a fundamental adaptive behaviour of the nervous system appearing as a response decrement to repeated stimulation. It does not involve the decrease in peripheral receptor activity which happens during sensory adaption and fatigue. It allows for selection of important information among other stimuli and is involved in learning and memory. 6. Magis D, Lisicki M, Coppola G. Highlights in migraine electrophysiology: are controversies just reflecting disease heterogeneity? Curr Opin Neurol. 2016;29(3):320-30, 11. Rankin CH, Abrams T, Barry RJ, Bhatnagar S, Clayton DF, Colombo J, et al. Habituation revisited: an updated and revised description of the behavioral characteristics of habituation. Neurobiol Learn Mem. 2009;92(2):135-8.

The variations in neurophysiology between migraine phases suggest that longitudinal studies are advantageous compared to cross-sectional studies to detect differences between phases (16), but such studies have seldom been performed. One recent cross-sectional study on motor evoked potentials (MEP) with repetitive transcranial magnetic stimulation showed findings suggesting a preictal increase in threshold for activating inhibitory homeostatic mechanisms which possibly corresponds to a theory of preictal hypoactivity (17). Furthermore results suggesting lowered thresholds for inhibitory responses were found in the ictal phase, possibly supporting a theory of ictal increase in cortical excitability (17). Another recent study on sensorimotor cortex done with magnetoencephalography (MEG) found results supporting ictal hyperexcitability in ipsilateral sensorimotor cortices. This observation was interpreted as a spread of abnormal ictal brain activation triggered by movements, which may play an important role in the attack cascade (10). However, many of the formerly used techniques only to a limited extent measure the rhythmicity generated by the thalamocortical systems specifically. A technique assumed to specifically render a representation of the excitability controlling thalamocortical rhythmicity is event-related desynchronization and synchronization (ERD/ERS) (18).

ERD/ERS is a neurophysiological phenomenon defined as a frequency specific decrease or increase in EEG activity, represented as power (μV^2) in the EEG. ERD/ERS represents an induced, time-locked, non-phase-locked response to an event. It is assumed that this response is a result of decreased or increased synchrony of firing in underlying neuronal populations. More specifically, the ERD/ERS represents changes in the activity of local interactions between thalamocortical projection neurons and cortical interneurons which controls the frequency of the EEG (18). ERD/ERS consequently reflects different neurophysiological properties for different cortical areas and different frequency bands.

Post-movement beta ERS (PMBS) over sensorimotor cortices is one relatively robust ERD/ERS-subtype with good signal to noise ratio (18). The maximum of the PMBS is documented to coincide with a reduced excitability of motor cortex neurons and hence the PMBS may be related to a deactivated state of motor cortex (18-20). Furthermore the PMBS increase in beta power is also suggested to reflect an active inhibition of the motor cortex by somatosensory afferents from joint receptors, muscular spindles and/or cutaneous receptors (21-23).

The aim of the present controlled longitudinal blinded study was to evaluate PMBS in sensorimotor cortex for migraine patients with both a purely motor and a more complex sensorimotor task that would engage more somatosensory afferents. To our knowledge PMBS has not been studied previously in migraine patients. First, to test the hypothesis that migraine patients have lowered thalamocortical drive, and consequently increased PMBS interictally, PMBS was compared between healthy controls (CO) and migraine patients (MIG). Second, to test the hypothesis that migraine patients have preictal and ictal changes in sensorimotor cortical excitability, paired intraindividual PMBS changes were evaluated for preictal-interictal, ictal-interictal and postictal-interictal differences.

Subjects and methods

Subjects

We included 41 migraine patients and 31 healthy controls. Migraine patients were recruited by a newspaper advertisement and subsequently screened via telephone by nurses trained in headache research. Thereafter a neurologist evaluated 52 migraine patients for inclusion according to the International Headache Society classification of headache disorders, 2nd edition: Migraine without aura (MwoA, 1.1, 33 patients included) and typical aura with migraine headache (MA, 1.2.1, 8 patients included). The study group consisted of men and women aged 18-65 years with 2-6 migraine attacks each month for the last 3 months, who did not use prophylactic medication. Healthy controls were recruited among blood donors. Before inclusion the controls underwent a semi-structured interview by an experienced nurse.

Exclusion criteria for both migraine patients and controls were the following: Coexisting frequent episodic or chronic tension-type headache, acute or chronic neurological disease, connective tissue disorders or other painful conditions, malignancy, previous craniotomy or cervical spine surgery, cardiopulmonary or cerebrovascular disease, hypertension, pregnancy, medication for acute or chronic pain, use of neuroleptics, alcohol or drug abuse, ferromagnetic implants, and use of neuroactive substances like anti-depressive, anti-epileptic, or migraine prophylactic drugs within 4 weeks before the test.

Demographic data on all subjects were recorded in addition to clinical presentation of the migraine patients by a questionnaire and a semi-structured interview. Every migraine patient also completed a headache diary from 2 weeks before inclusion until 2 weeks after the last EEG recording. Data registered included pain characteristics, accompanying symptoms, consequences for work and leisure, and time of start and end of headache. This allowed for classification of the headache and its relationship in time to the EEG recordings. Recordings were classified as preictal (< 36h before attack), postictal (< 36h after attack), ictal (pain attack) and interictal (> 36h from attack). Patients with both an attack-related recording and an interictal recording were included in migraine subgroups for paired analysis.

Each subject went through three EEG recordings except for one migraine patient who abstained from undergoing all recordings because headache worsened after the tests. Hence this subject only underwent two tests.

Staff involved in data reduction and analysis was blinded regarding to the diagnostic status of the subjects. The subjects received NOK 1000 (about EUR 106 with current exchange rates) as compensation to cover expenses after completing all three recordings (not mentioned in the advertisement). Written consent was obtained by all subjects.

EEG Recordings and experimental setup

EEG recordings were performed at the same time of day with 3-10 days intervals, during the years 2004 and 2005. Approximately 30 min EEG was recorded with eyes closed. The first 5 minutes were undisturbed relaxed wakefulness, followed by a motor/sensorimotor test and thereafter photo stimulation trains. Based on the first and last recording periods, resting state quantitative EEG and steady state visual evoked potential results have been reported previously by Bjørk et al.(9, 16, 24, 25). The present paper evaluates PMBS-data from the motor and sensorimotor tests, which have not previously been analysed.

Twenty four scalp electrodes were attached according to the 10/20 international system (26) with channels for lateral anterior temporal electrodes, horizontal and vertical eye movements, and ECG. EEG was recorded digitally in Nervus 3.0 with M40 amplifier and common reference with 256 Hz sampling rate. Average reference montage was used with low- and high-pass filter of 0.5 and 70 Hz in addition to notch filter (50 Hz). To avoid drowsiness the subjects were asked to open their eyes every minute as well as being talked to by the technician if drowsiness occurred during the first five minutes of the EEG-recording.

Each subject performed both a motor test (M) and a sensorimotor test (SM) with approximately 30 repeated movements in each test. The order of tests was randomized for each subject, and fixed for each day of recording for the same subject. The instructions given to all subjects were the following. Each test would last about 8 minutes with a light blink indicating when to start each movement. For the motor test subjects were to first flex their wrist for 2 seconds, then extend their wrist for 2 seconds, followed by about 15 seconds of relaxation. For the sensorimotor test an identical flexion-extension movement was performed, however, a bowl of different material spheres (wood or metal) was placed about 5 cm below the neutrally positioned fingers so that the fingers were in contact with the spheres in the flexed position. The task was to use the 2 seconds in the flexed position to scan spheres lightly with their fingertips to detect if a sphere of wood was present in the bowl or not. The

right arm was used in both sequences. Two EMG-channels for flexion and extension were included in the EEG recording for determination of movement epochs (Figure 1).

ERD/ERS analysis

IIR-filtered data in the 12-19 Hz beta frequency band (27, 28) were calculated for each test and used for the PMBS analysis. EEG-data in 256 Hz resolution were exported from sensorimotor cortices electrodes C3 (left side, contralateral) and C4 (right side, ipsilateral) because previous PMBS-studies have found maximal responses close to the central sulcus (18, 29, 30). The amplitude was squared to obtain power and then averaged across all movements within the same test (18). Movement onset and offset were marked (Figure 1) and used to determine epochs for analysis. Time-power graphs for all subjects were visually inspected by a blinded researcher to determine response timings used to select epochs for analysis. Selections from -3 to -1 second prior to start of movement were used as baseline. This choice was considered advantageous over a baseline prior to end of movement as the movement period consisted of multi directional movement of varying duration, with possibly different ERD/ERS responses during movement duration (31).

The post-movement period was defined from 1 to 3 seconds after movement offset (based on blinded, visual inspection of power-time graphs for every subject). PMBS has mostly been reported to peak within the first second after termination of voluntary movement (18, 21, 32). However a later interval was more appropriate for the present protocol. The selections were made blinded, before data were analysed. The natural logarithm of average power in the post-movement period divided by average power in baseline was calculated as our main PMBS-variable (the "averaged response"). A moving average dataset was also calculated for 30 data points per time-window in order to smooth the data and reduce the point-to-point variability before a secondary PMBS-variable, the maximal response amplitude, was calculated (18). The natural logarithm of this maximal value in the active period divided by the maximal value of the baseline period was calculated as the "peak response".

Statistical analysis

For each migraine patient one test was selected for each cyclic phase that was available (interictal, preictal, ictal and postictal). If several tests for the same cyclic phase were available, the second was chosen. Control EEGs were chosen to have a similar test-order distribution as the interictal migraine group.

We conducted repeated measures ANOVA (R-ANOVA) with within-subject factors “side” (C3 vs C4) and “SM/M” (sensorimotor vs motor test), and between-subjects factor “group” (CO vs MIG). This was done in order to evaluate differences between the groups in the interictal phase. Post-hoc two sample Student’s t-test was used to further evaluate significant factors regarding the detailed nature of the differences between diagnostic groups. One sample Student’s t-test, was used to ensure that PMBS responses were present, i.e. ratios greater than 1.

Three R-ANOVAs within the migraine group were carried out with the factors “phase” (separate R-ANOVAs with preictal-interictal, ictal-interictal and postictal-interictal), “side” (C3 vs C4) and “SM/M” (sensorimotor vs motor test). We also conducted post-hoc paired t-tests for each variable to evaluate the detailed nature of the significant R-ANOVA factors.

Variables with significant group or phase differences were examined visually for possible outliers. A few (n=6) tests with outlying data points and artefactual response-peaks were replaced with a test from another day in the same category test (ictal, pre-, post-, or inter-ictal) if available from the same subject, or else the artefactual test was excluded from analysis (control n=1; preictal migraine n=1); leaving 30 controls for the final comparison with interictal migraine and 11 patients for the paired within-subject preictal-interictal analysis.

Results

Demographic and clinical data in controls, interictal migraine groups and paired subgroups are displayed in Table 1 and Table 2.

Interictal analyses between migraine patients and control

Grand mean beta power-time graphs for baseline and post-movement are shown in Figure 2 suggesting a slightly earlier PMBS for patients than controls. However, for the chosen response variables, the main effects of *Group* were not significant (Table 3). As expected, PMBS was larger on the contralateral side (Table 4) with a highly significant main effect for *Side* (Table 3). In addition, no significant *Group*-interactions were seen (Table 3), indicating essentially identical PMBS in interictal migraine compared to headache-free control subjects. Averaged response and peak response distributions were similar in migraine and controls for both sites and conditions (Table 4).

Paired analyses for preictal, ictal and postictal phases compared to the interictal period

Paired analysis with repeated measures ANOVA (Table 5) reveals a highly significant interaction between *Side* (C3 vs C4) and preictal cyclic *Phase* (preictal vs interictal). The preictal interaction was consistent between the two response-variables (Averaged response, $F(1,10) = 21.6$, $p = 0.001$; Peak response, $F(1,10) = 19.7$, $p = 0.001$). There is also a significant interaction (Averaged response, $F(1,12) = 5.0$, $p = 0.045$) between *Side* (C3 vs C4) and ictal cyclic *Phase* (ictal vs interictal) (Table 5). The main effect of *Side* was as expected also in general significant.

Paired post-hoc t-test (Table 6) revealed a significantly lower averaged PMBS response for ictal than interictal phase (ictal mean ratio = 1.17; interictal mean ratio = 1.33; $p = 0.045$) at the ipsilateral side (C4) for the sensorimotor test. A strong tendency towards a higher PMBS in preictal than interictal phase was also seen (preictal mean ratio = 1.65; interictal mean ratio = 1.43; $p = 0.058$). However C3-C4 difference for sensorimotor test is highly significant ($p=0.001$) between preictal and interictal phase. Figure 3 illustrates that the mean PMBS ratio at C4 is large in the preictal phase and lower in the ictal phase, while the corresponding difference is lower at C3.

Discussion

Main findings

The main finding in this blinded longitudinal study was a highly significant preictal interaction between *Side* (C3 contralateral vs C4 ipsilateral) and *Phase* (preictal vs interictal) for both averaged response and peak response. PMBS was elevated at C4 preictally in comparison to the interictal phase after the sensorimotor test, while this preictal-interictal difference was reversed for the motor test at C3.

Another significant finding was the interaction between *Side* (C3 contralateral vs C4 ipsilateral) and *Phase* (ictal vs interictal) for averaged response. Post hoc paired t-test revealed a significantly lowered PMBS at ipsilateral C4 after the sensorimotor test ictally compared to the interictal phase.

No significant differences were found between controls and migraine patients in the interictal phase, but apparent differences in the grand-mean time graphs suggest that a different analytical approach with briefer time-intervals (20, 32) might reveal subtle changes that could not be detected by our response variables.

Result interpretation

Based on these results the working hypothesis that migraine patients have increased PMBS interictally compared to healthy controls could not be confirmed. Paired results confirm the hypothesis that migraine patients have altered preictal and ictal PMBS. Since PMBS may be related to a balance between inhibition from somatosensory afferents and intracortical inhibition (21, 23, 33), it is probably the level of cortical inhibition that is subject to cyclic modulation. This modulation, regulating the overall cortical excitability, may play a role in migraine attack initiation and continuation. In this study, relative normalization of PMBS, and presumably also of intracortical inhibition and overall cortical excitability, seems to have occurred in the postictal phase.

The results in this study are not able to support the current belief that the migraine brain has altered excitability in the interictal phase (6) although a more detailed analysis of the PMBS time-course may reveal more subtle changes. In addition, the cyclic change seen in our study does not support that excitability levels are normal very close to the migraine attack (15), but rather suggest that preictal excitability is decreased and followed by increased ictal

excitability. This result was only seen at the ipsilateral motor area, suggesting abnormal spread of activation from contralateral to ipsilateral side. Moreover, the effect was only observed for a more complex task involving more tactile stimulation in addition to the movement-related afferent activity evoked by the motor wrist flexion-extension that was integral to both tasks. It is accordingly possible that the active inhibition from sensory afferents to motor cortex is affected very close to the attack, facilitating abnormal spread of activation from the left to the right side.

A recent 5 Hz repetitive transcranial magnetic stimulation (rTMS) study on hand motor evoked potential (MEP) amplitudes also found preictal hypoexcitability (presumed to be caused by increased thresholds for inhibitory mechanisms), followed by an ictal hyperexcitability (17). Furthermore, as somatosensory cortices are likely to be involved in sensory-discriminative aspects of pain (34), the preictal finding in the present study may be related to earlier findings of preattack pain hypersensitivity in migraine patients (35). However, it is not clear if our finding, increased preictal PMBS, really represent a general increase in net cortical inhibition, i.e. hypoexcitability. Possibly, PMBS reflects modulation of presynaptic control or changes in the basic excitatory thalamocortical drive. Cortical hypofunction, affecting top-down inhibitory gating mechanisms, may also render the migraine brain more sensitive to external stimuli, and possibly contribute to the onset of a migraine attack (34).

PMBS of smaller magnitude in patients with Parkinson's disease compared to controls has earlier been interpreted to represent impaired cortical recovery after movement (18, 36). Investigation of PMBS in patients with restless leg syndrome revealed increased PMBS at contralateral C3, interpreted as a higher need for cortical inhibition due to increased cortical excitation (37). One study on patients with amyotrophic lateral sclerosis have found reduced PMBS in ipsilateral cortex compared to controls and interpreted it as impaired interhemispheric inhibition (38). Patients with neuropathic pain related to sensory deafferentation have shown significant differences between PMBS patterns related to the painful side compared to the normal side, and painful side beta ERS was more restricted to the ipsilateral side (33), resembling our preictal C4 findings. Possibly our findings support an older theory about "functional sensory deafferentation" as part of migraine pathophysiology (39).

Study limitations

There are several methodological aspects to consider in this study design. This study used multi directional movement to analyse movement related responses with sensory discrimination. Multi directional, self-paced movement of different duration both inter- and intraindividually may lead to ERD from one movement occurring simultaneously as ERS from another movement (31). PMBS can also be calculated with either a baseline set before start of movement or before end of movement. Because the responses during movement in the present study may vary with the variable duration of the multi directional movements between single repetitions, we chose to use a pre-movement onset baseline for PMBS calculation.

Baseline must also be chosen before the subject initiates a plan to execute the next movement. Studies on lower beta band movement-ERD suggest that ERD starts about 2 seconds prior to self-paced movement onset in the contralateral Rolandic region (18). Light blinks were used in this study as triggers to control the start of the event related response and in the vast majority of repetitions the movement was initiated within 1 second after the light blink. Hence, the results are probably not influenced by this baseline although a recalculation with a -2 to -4 second baseline could be considered.

The post-movement period was defined from 1 to 3 seconds after movement offset which differs slightly from other studies who have reported PMBS to peak within the first second after termination of voluntary movement (18, 21, 32). However, these studies vary in design from ours by using self-paced movement initiation, source-derivation reference as opposed to average reference and briefer movements. The correlation between mechanical movement offset and EMG offset has also been discussed in other studies and their possible difference in relation to the timing of PMBS (21), possibly suggesting different timings to be used for different study designs. A later interval than most often used was more appropriate for the present protocol. Movement duration is considered not to affect PMBS; hence the movement duration in the present study should be of little significance (22, 32).

Earlier studies have also used up to 70-80 repetitions of movements (32) which is considerably higher than what is used in this study (up to 30 repetitions) and may play a role in the limitation of variance in averaging across movement repetitions and tests. Handedness of subjects is not taken into further consideration as the vast majority of subjects were right handed and this aspect does not affect paired evaluations.

We chose to use only one main variable for the PMBS response although two electrodes and two conditions may render the study somewhat vulnerable to type 1 errors. However, as all sites and conditions were combined in ANOVA models, type 1 errors are less likely than in multiple testing. An *a priori* selected beta band of 12-19 Hz (27, 28) was also used to further avoid type 1 errors (40). It should also be mentioned that paired subgroups were rather small, suggesting that type II errors, preventing our design to detect small effects, may also have occurred. Further larger longitudinal studies on migraine brain neurophysiology in different study populations are needed to replicate our findings and draw strict conclusions.

Conclusion

The cyclic changes in PMBS for migraine patients may indicate that a dysfunction in sensorimotor cortex is involved in the migraine attack cascade. Current understanding of the PMBS phenomenon suggests that it is the level of cortical inhibition that is subject to cyclic modulation. This modulation, regulating the overall cortical excitability, may play a role in migraine attack initiation and continuation. Elevated ipsilateral PMBS levels preictally and lowered ipsilateral PMBS ictally may consequently represent asymmetric cyclic changes, from somatosensory hypo- to hyperexcitability, as a result of alterations in basic cortical inhibitory mechanisms. Normalization of these changes seemed to occur in the postictal phase. Longitudinal studies, including studies with drug interventions, are advised to further examine these cyclic changes in cortical sensorimotor properties in migraine.

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Tables and figures

Table 1 Demographic and clinical data on groups used in interictal analysis (25)

	Migraine *(n = 33)*	Controls *(n = 30)*
Women/men	30/3	27/3
MwoA/MA	27/6	
Age (years)	36.5 (12.7)	39.7 (11.5)
Days from last menstruation	11.0 (9.3)	9.3 (8.5)
Headache history (years)	19.3 (11.0)	
Headache days last 3 months	6.2 (4.0)	
Headache intensity (0-4)	2.4 (0.7)	
Headache duration (h)	17.8 (22.0)	
Photophobia (0-2)	1.4 (0.7)	
Phonophobia (0-2)	1.1 (0.8)	

MA = migraine with aura, MwoA = migraine without aura. Mean (SD) or numbers.

Table 2 Demographic and clinical data on subgroups used in paired analysis (16)

	Preictal *(n = 11)*	Ictal *(n = 13)*	Postictal *(n = 9)*
Women/men	11/0	12/1	7/2
MwoA/MA	9/2	10/3	8/1
Age (years)	37.3 (12.9)	37.5 (12.5)	41.3 (12.8)
Headache history (years)	20.5 (11.7)	20.5 (9.9)	18.1 (13.1)
Headache days last 3 months	6.7 (4.8)	7.2 (4.7)	4.2 (2.3)
Heacache intensity (0-4)	2.4 (0.7)	2.3 (0.6)	2.2 (1.0)
Headache duration (h)	15.9 (20.2)	14.9 (17.3)	18.4 (30.5)
Photophobia (0-2)	1.4 (0.7)	1.0 (0.8)	1.2 (0.7)
Phonophobia (0-2)	1.2 (0.7)	0.8 (0.8)	1.2 (0.8)

Mean (SD) or numbers. Subgroups with both an interictal EEG recording (> 36 h from attack) and a preictal(< 36 h before attack), ictal or postictal (< 36 h after attack) EEG recording (16).

Table 3 Repeated measures ANOVA. Interictal migraine patients compared to headache-free controls.

	Averaged response		Peak response	
Within subjects effects	F(1,61)	p	F(1,61)	p
Side	36.3	**<.0005**	21.8	**<.0005**
SM/M	.1	.76	.6	.44
Side * SM/M	.6	.45	.1	.77
Side * Group	.1	.78	.7	.42
SM/M * Group	1.0	.32	2.5	.12
Side * SM/M * Group	.1	.77	.0	.90
Between subjects effect	F(1,61)	p	F(1,61)	p
Group	.1	.74	.1	.72

Averaged response is the ratio between mean power in the interval from 1 to 3 sec after movement offset and mean power in the interval 3 to-1 sec before movement onset (baseline). Peak response is the corresponding ratio between maximal values in the same intervals. Ratios were LN-transformed before statistical analysis. Within subject factors used were side (C3 vs C4) and SM/M (sensorimotor vs motor). The between subjects factor is Group (migraine vs controls).

Table 4 Post-movement beta synchronisation mean response/baseline ratios for the averaged response and the peak response.

Averaged response	Mean ratio (±sd retransformed)				
	Migraine	Control	t	df	p
C3 SM	1.74 (1.25-2.44)	1.85 (1.28-2.69)	.69	58.7	.49
C3 M	1.78 (1.14-2.78)	1.73 (1.21-2.47)	-.27	59.9	.79
C4 SM	1.42 (1.08-1.87)	1.52 (1.02-2.28)	.78	50.7	.44
C4 M	1.47 (1.01-2.14)	1.47 (1.04-2.09)	.00	60.9	.99

Peak response	Mean ratio (±sd retransformed)				
	Migraine	Control	t	df	p
C3 SM	1.84 (1.23-2.76)	2.02 (1.27-3.23)	.86	57.7	.39
C3 M	1.92 (0.99-3.70)	1.74 (1.12-2.71)	-.69	56.3	.49
C4 SM	1.44 (1.05-1.96)	1.68 (0.93-3.03)	1.40	45.5	.17
C4 M	1.51 (0.90-2.53)	1.49 (0.89-2.50)	-.13	60.3	.90

Averaged response is the ratio between mean power in the interval from 1 to 3 sec after movement offset and mean power in the interval 3 to 1 sec before movement onset (baseline). Peak response is the corresponding ratio between maximal values in the same intervals. Ratios were LN-transformed before statistical analysis and retransformed to mean ratios and mean ± SD for tabulation.

Post-hoc two-sample Student's t-tests (equal variance not assumed) are included. EEG from central electrodes C3 (left) and C4 (right). SM = sensorimotor test, M = motor test.

Table 5 Repeated measures ANOVA paired analysis with cyclic phase (preictal, ictal and postictal).

Averaged response						
Within subjects effects	Preictal		Ictal		Postictal	
	F(1,10)	p	F(1,12)	p	F(1,8)	p
Phase	.7	.44	.0	.85	.0	.96
Side	5.5	**.041**	6.9	**.022**	6.0	**.040**
SM/M	.0	.98	.3	.58	1.5	.25
Side * SM/M	.0	.87	.8	.40	.1	.78
Side * Phase	21.6	**.001**	5.0	**.045**	.7	.42
SM/M * Phase	.6	.48	.3	.57	.0	.99
Side * SM/M * Phase	4.2	.07	5.2	**.043**	2.2	.18

Peak response						
Within subject effects	Preictal		Ictal		Postictal	
	F(1,10)	p	F(1,12)	p	F(1,8)	p
Phase	.0	.84	.0	.97	.0	.90
Side	7.0	**.025**	3.4	.09	4.6	.06
SM/M	.2	.64	.7	.41	1.6	.24
Side * SM/M	1.3	.28	1.0	.34	.2	.71
Side * Phase	19.7	**.001**	2.1	.17	.1	.84
SM/M * Phase	.7	.43	.7	.43	.9	.38
Side * SM/M * Phase	.4	.56	.5	.51	.7	.42

Paired analysis of subgroups preictal(< 36 h before migraine pain attack), ictal and postictal (< 36 h after migraine pain attack). Factors used were side (C3 vs C4), SM/M (sensorimotor vs motor) and cyclic phase (preictal-interictal, ictal-interictal and postictal-interictal).

Table 6 Paired t-test for preictal-interictal, ictal-interictal and postictal-interictal periods.

Averaged response	Mean ratio (±sd retransformed)			Peak response	Mean ratio (±sd retransformed)		
C3 Sensorimotor	Interictal	Compared period	p	C3 Sensorimotor	Interictal	Compared period	p
Preictal	1.74 (1.26-2.42)	1.81 (1.23-2.67)	.64	Preictal	2.02 (1.22-3.33)	2.07 (1.05-3.90)	.98
Ictal	1.54 (1.06-2.23)	1.61 (1.12-2.33)	.45	Ictal	1.53 (1.02-2.29)	1.47 (0.88-2.44)	.67
Postictal	1.78 (1.39-2.28)	1.76 (1.12-2.75)	.90	Postictal	1.94 (1.32-2.85)	1.71 (1.02-2.87)	.27
C3 Motor				C3 Motor			
Preictal	1.87 (1.30-2.70)	1.67 (1.18-2.36)	.25	Preictal	1.97 (0.95-4.05)	1.61 (1.06-2.44)	.28
Ictal	1.59 (1.08-2.34)	1.64 (1.02-2.63)	.83	Ictal	1.58 (0.83-3.01)	1.84 (0.93-3.62)	.53
Postictal	1.51 (0.96-2.38)	1.59 (1.26-2.01)	.73	Postictal	1.94 (1.32-2.85)	1.73 (1.16-2.57)	.57
C4 Sensorimotor				C4 Sensorimotor			
Preictal	1.43 (1.04-1.96)	1.65 (1.17-2.32)	**.058**	Preictal	1.39 (0.93-2.06)	1.70 (1.11-2.62)	.14
Ictal	1.33 (1.07-1.64)	1.17 (0.88-1.56)	**.045**	Ictal	1.37 (1.00-1.87)	1.23 (0.77-1.99)	.37
Postictal	1.47 (1.02-2.13)	1.48 (0.96-2.29)	.93	Postictal	1.55 (1.12-2.14)	1.53 (0.96-2.43)	.92
C4 Motor				C4 Motor			
Preictal	1.45 (1.09-1.94)	1.64 (1.19-2.25)	.28	Preictal	1.53 (0.89-2.64)	1.65 (1.19-2.29)	.65
Ictal	1.32 (0.99-1.76)	1.31 (0.90-1.91)	.96	Ictal	1.37 (0.83-2.26)	1.34 (0.79-2.28)	.90
Postictal	1.37 (0.97-1.93)	1.29 (1.01-1.64)	.66	Postictal	1.27 (0.90-1.79)	1.34 (1.01-1.78)	.69

Averaged response is the ratio between mean power in the interval from 1 to 3 sec after movement offset and mean power in the interval 3 to-1 sec before movement onset (baseline). Peak response is the corresponding ratio between maximal values in the same intervals. Ratios were LN-transformed before statistical analysis and retransformed to mean ratios and mean ± SD for tabulation. Post-hoc paired Student's t-tests are included. EEG from central electrodes C3 (left) and C4 (right) for the sensorimotor test and motor test.

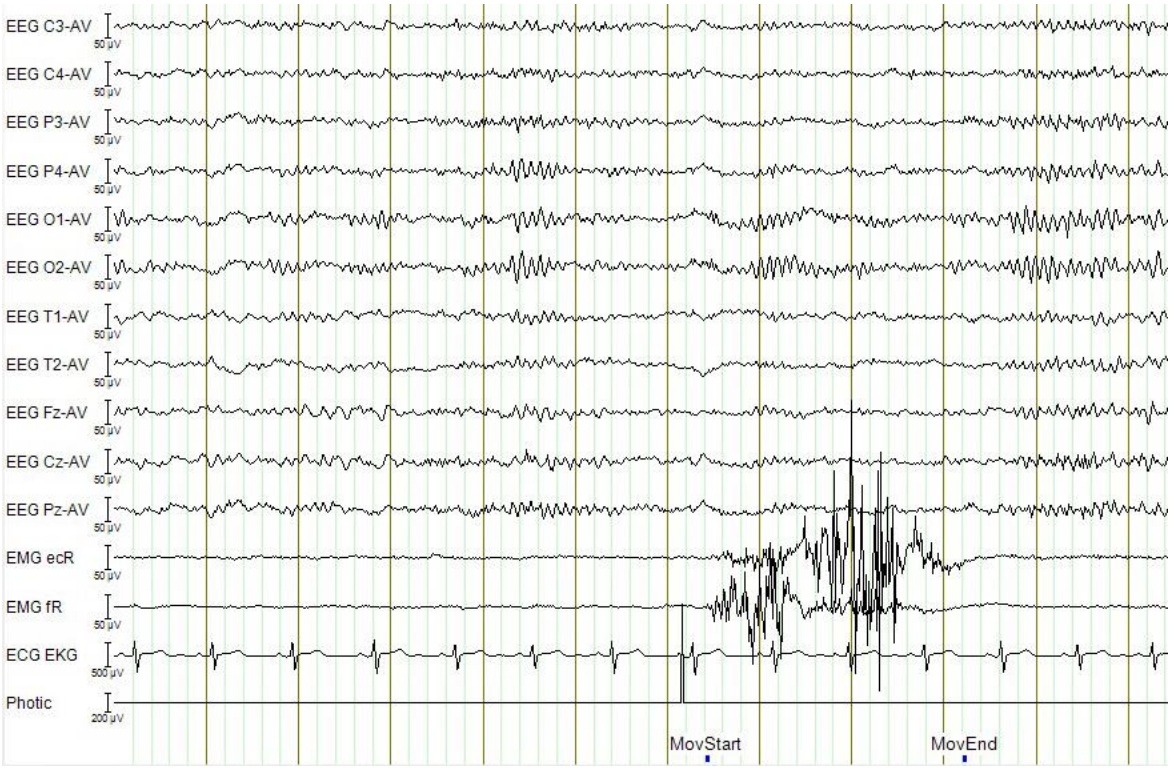

Figure 1. Example from one single movement with EEG, EMG (ecR: radial wrist extensors, fR: forearm wrist flexors), and ECG channels. The photic channel marker represents a light blink as a sign for the subject to prepare for executing the task. "MovStart" and "MovEnd" markers were placed manually at the start and the end of EMG-movement.

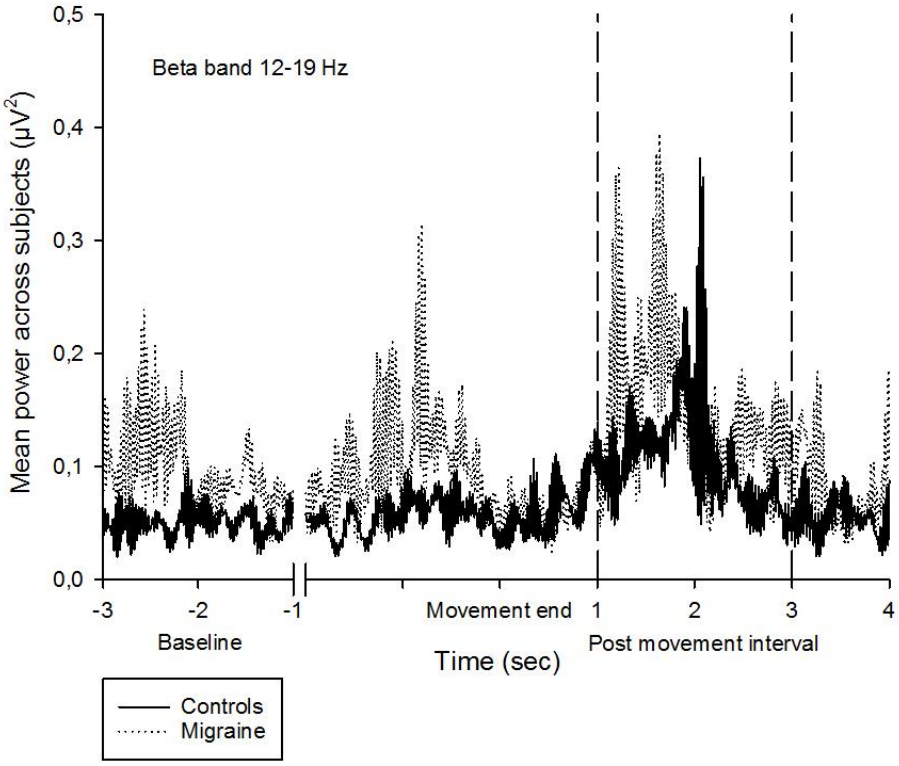

Figure 2. Grand mean power across subjects at the contralateral C3 electrode for the sensorimotor task in controls and interictal migraine patients. First two seconds (-3 to -1) represent pre-movement onset baseline. Broken vertical lines indicate the selected interval (1 to 3 seconds) for the post-movement period.

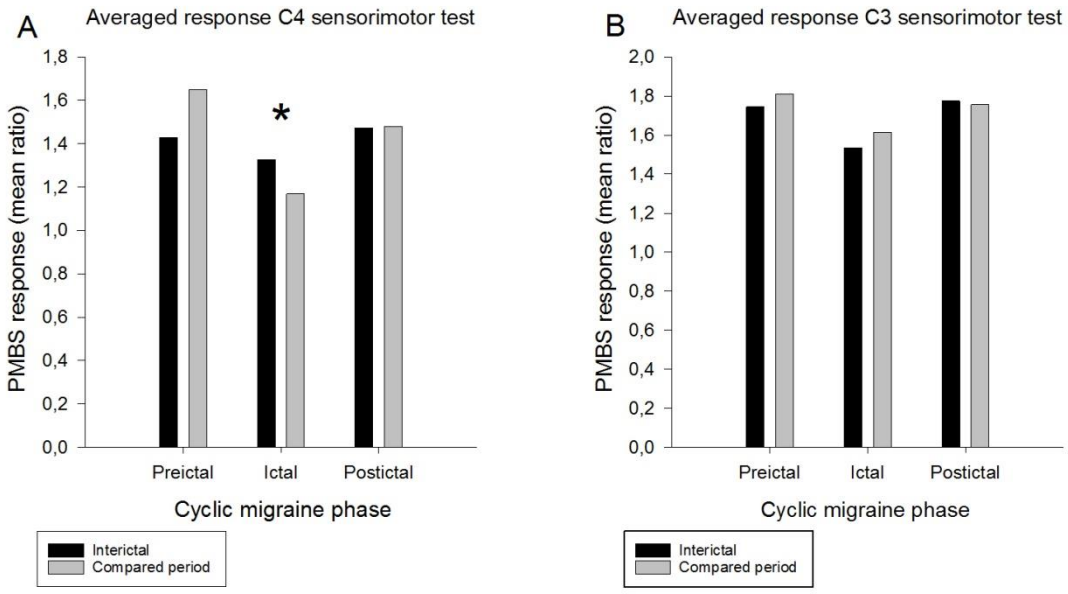

Figure 3. Averaged PMBS response to the sensorimotor task in paired migraine subgroups. The LN-transformed response variable has been retransformed to a mean ratio (post-movement/baseline) for tabulation and graphic display. (A) PMBS response for ipsilateral C4. Significant difference with paired t-test in the ictal phase compared to the interictal phase (ictal mean ratio = 1.17; interictal mean ratio = 1.33; p = 0.045) (*). Tendency towards difference with paired t-test in the preictal phase compared to the interictal phase (preictal mean ratio = 1.65; interictal mean ratio = 1.43; p = 0.058). However C3-C4 difference for sensorimotor test is highly significant (p=0.001) between preictal and interictal phase. (B) PMBS response for contralateral C3. No significant differences seen in paired t-test.