



Headache Related Alterations of Visual Processing in Migraine Patients

Marco Lisicki,^{*,1} Kevin D'Ostilio,^{*,1} Gianluca Coppola,[†] Romain Nonis,^{*} Alain Maertens de Noordhout,^{*} Vincenzo Parisi,[†] Delphine Magis,^{*,2} and Jean Schoenen^{*,2}

^{*}Headache Research Unit, CHR Citadelle Hospital, CHU de Liège, University of Liège Belgium, [†]IRCCS - Fondazione Bietti, Research Unit of Neurophysiology of Vision and Neurophthalmology, Rome, Italy

Abstract: Migraine is characterized by an increased sensitivity to visual stimuli that worsens during attacks. Recent evidence has shown that feedforward volleys carrying incoming visual information induce high-frequency (gamma) oscillations in the visual cortex, while feedback volleys arriving from higher order brain areas induce oscillatory activity at lower frequencies (theta/alpha/low beta). We investigated visually induced high (feedforward) and low (feedback) frequency activations in healthy subjects and various migraine patients. Visual evoked potentials from 20 healthy controls and 70 migraine patients (30 interictal and 20 ictal episodic migraineurs, 20 chronic migraineurs) were analyzed in the frequency domain. We compared power in the theta-alpha-low beta and gamma range between groups, and searched for correlations between the low-to-high frequency activity ratio and number of monthly headache and migraine days.

Compared to healthy controls, interictal migraine patients had increased visually induced low frequency (feedback) activity. Conversely, ictal and chronic migraine patients showed an augmented gamma band (feedforward) power. The low-frequency-to-gamma (feedback/feedforward) activity ratio correlated negatively with monthly headache days and tended to do so with migraine days. Our findings show that visual processing is differentially altered depending on migraine cycle and type. Feedback control from higher order cortical areas predominates interictally in episodic migraine while migraine attacks and chronic migraine are associated with enhanced incoming afferent activity, confirming their similar electrophysiological profile. The presence of headache is associated with proportionally higher gamma (feedforward) activities.

Perspective: This study provides an insight into the pathophysiology of migraine headache from the perspective of cortical sensory processing dynamics. Patients with migraine present alterations in feedback and feedforward visual signaling that differ with the presence of headache.

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¹These authors equally participated in this study.

²These authors contributed equally to the supervision of the study.

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Address reprint requests to Prof Jean Schoenen, MD, PhD, University of Liège, University Department of Neurology, CHR Citadelle Hospital, Boulevard du 12eme de Ligne 1, 4000 Liège, Belgium. E-mail: jschoenen@uliege.be

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It is well established in healthy humans that marked changes in brain rhythmic oscillatory activity over a wide range of frequency bands are related to pain processing.^{30,32} This also applies for head pain associated to migraine. Several electrophysiological studies have shown that migraine is a brain disorder characterized by an abnormal corticosubcortical oscillatory activity that fluctuates along the migraine cycle, differs between the ictal and interictal intervals,^{7,12,34,35,46} and remains persistently altered as the disease chronifies.⁸

According to available experimental evidence, oscillations in the alpha and gamma frequency bands can be used as direct, objective, experimentally stable, and interrelated measures of cognitive and sensory brain tasks. During ongoing pain alpha power is reduced and gamma power is increased in several brain regions,^{17,18,45} including posterior cortical areas.^{4,5} Similar modifications correlate with active selection and integration of relevant unattended visual information, resulting from the balance between feedforward volleys reaching the visual cortex from the lateral geniculate nucleus (fast gamma oscillations) and feedback activity coming from higher order visual areas (low-frequency (theta/alpha/low beta) oscillations).^{24,28} Spectral analysis allows to easily identify these 2 main frequency peaks (theta/alpha/low beta and gamma) in common scalp-recorded visual evoked potentials (VEPs), as confirmed by recent intracortical recordings in nonhuman primates as well as magnetoencephalographic studies in humans.^{24,28}

In this study we analyzed the previously described fluctuations of visual processing in migraine^{23,39} from the perspective of visually induced feedback (theta/alpha/low-beta) and feedforward (gamma) activations. We also tested whether these alterations in visual signalling were specifically associated with the frequency of full-blown migraine attacks, or if they were also related to the presence of mild tension-type like headaches, often present in migraineurs, particularly in those suffering from chronic migraine.

Subjects and Methods

Subjects

The study involved 90 participants: 20 healthy volunteers (HV), 30 episodic migraine without aura patients recorded during a headache-free interval (minimum 72 hours before or after an attack) verified on a headache diary and/or by a telephone call (EM), 20 ictal episodic migraineurs recorded during an attack (IM, 17 during the headache phase, 3 within 48 hours of the headache), and 20 chronic migraine patients without medication overuse (CM). Diagnoses were made in accordance with The International Classification of Headache Disorders 3rd edition beta version (ICHD3 beta).²⁰ HV did not report any first degree relative suffering from recurrent headaches of any type. Participants were consecutively recruited among University students or their families and via our headache clinic. Specifically, an announcement was posted in the University's intranet, and headache patients attending the consultation were personally invited to take part. Patients were not under any preventive treatment, nor had they been for the 3 preceding months. To ascertain the diagnosis, attack occurrence, and headache attacks severity, patients filled in a paper diary for ≥ 30 days in which headache intensity, associated symptoms (nausea, vomiting, photo-, phonophobia) and acute medication intake were registered. As in recent therapeutic trials,⁴¹ only headaches fulfilling the diagnostic criteria

for a migraine attack (International Classification of Headache Disorders 3rd edition beta version code 1.1) (unless they had been treated with a triptan) were considered migraine specific headaches. All other episodes of head pain were coded as unspecific headaches. None of the participants that initially agreed to participate were excluded afterwards. The study was approved by the Hospital's ethics committee (Centre Hospitalier Régional de la Citadelle, Liège, Belgium—protocol n° 1422) and conducted following the principles of the Declaration of Helsinki. All participants gave written informed consent.

Visual Evoked Potentials (VEP) Recordings and Analysis

VEP recordings were performed in the electrophysiology laboratory of the Headache Research Unit (Neurology Department, Centre Hospitalier Régional de la Citadelle, Liège, Belgium). All participants were studied in the morning, between 9 a.m. and noon. Subjects were sitting on a comfortable armchair, in a quiet room with dimmed light. A patch was placed over the left eye, and needle recording electrodes were introduced in the scalp at Oz (active) and Fz (reference) based on the 10–20 Electroencephalogram (EEG) system. During the recordings, subjects were instructed to maintain fixation on a red dot in the centre of a screen which displayed a black and white reversing checkerboard pattern (contrast of 80%, mean luminance 50 cd/m²). Temporal and spatial stimulating frequencies employed were 1.55 Hz (3.1 reversals/second) and 68, respectively. Six hundred epochs, each lasting 250 ms, were continuously recorded at a sampling rate of 5.000 Hz using a CED power 1401 device (Cambridge Electronic Design Ltd, Cambridge, UK). After DC subtraction, recordings were exported to EEGLAB,¹³ an open-source MATLAB (The MathWorks Inc) toolbox for electrophysiological signal processing, where they were band-pass filtered (low pass 100 Hz, high pass 1 Hz). Epochs whose amplitude exceeded a 2 standard deviations from the channel mean amplitude limit were considered artefacted and rejected (<6% of epochs). The Fast Fourier Transform was applied on each epoch to compute spectral decomposition. Log-transform of single-trial spectral power was performed before averaging. Data were zero-padded in order to increase frequency resolution to steps of 1 Hz. As in previous studies,²⁸ the 2 most prominent peaks of the spectrogram were observed in the theta/alpha/low beta 1) and gamma 2) frequency band ranges. To estimate power at these frequencies, the area under the curve (trapezoidal numerical integration; MATLAB function "trapz") of activity at each peak and nearby surrounding frequencies (4–16 Hz for theta-alpha-low beta and 40–60 Hz for gamma) was calculated for each individual (Fig 1). Considering the recent evidence showing that alpha-beta and gamma activity embedded in visually-induced cortical responses convey different information,^{24,28} and that

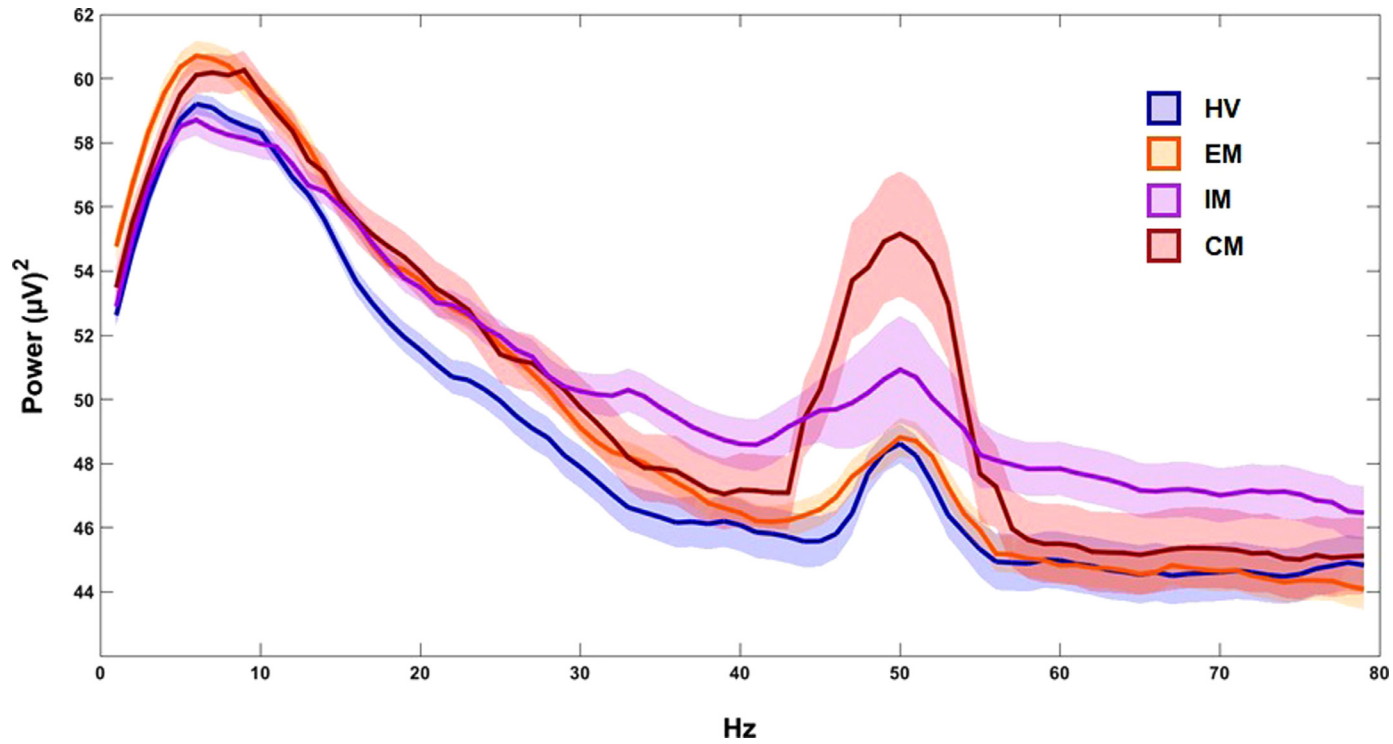


Figure 1. Power (μV^2) in the various frequency bands (Hz). Median power (bold line) \pm standard error (shaded area) is depicted for each group. Healthy volunteers (HV-blue) showed the lowest mean power at all frequencies. Episodic migraine patients (EM-orange) have the highest alpha power values, while gamma power is greatest among chronic migraine patients (CM-red), followed by ictal episodic migraine patients (IM-magenta). (Color version available online.)

Table 1. Participants' Characteristics. Mean Monthly Migraine Days and Headache Days Did Not Differ Significantly Between Episodic Migraine Patients in the Interictal and Ictal Periods

	HEALTHY VOLUNTEERS		INTERICTAL EPISODIC MIGRAINE		ICTAL EPISODIC MIGRAINE		CHRONIC MIGRAINE		P VALUE
Age (mean \pm SD)	36.1	11.4	33.3	11.9	32.7	9.1	40.3	12.7	$P = .126$
Female percentage	75%		90%		100%		95%		$P = .051$
Disease duration (mean \pm SD)			14.6	9.4	15.7	11.8	18.75	11.8	$P = .430$
Monthly migraine days (mean \pm SD)			5.5	3.5	5.9	3.6	15.8	6.4	$P < 0.001$
Monthly headache days (mean \pm SD)			7.3	4.1	8.6	6.6	23.9	5.7	$P < .001$

abnormal visual responsiveness in migraine is the result of a complex process involving several cortical areas,²⁷ we calculated the low frequency-to-gamma activity ratio as a measure of the interaction between simultaneous volleys reaching the visual cortex. In addition, considering the overlap between visually induced cerebral gamma activity and the frequency spectrum of different possible sources of contamination of the signal (muscular artefacts, AC line noise) we performed a supplementary analysis of event related spectral perturbations which permits to visually inspect changes in the power spectrum throughout time. Investigators in this study were not blinded to diagnosis, but all electrophysiological analyses were fully automated.

Statistical Analysis

Statistical analyses and graphs were performed in Prism version 6.00 for Windows (GraphPad Software, La Jolla, CA). The assumption of normal distribution was assessed using the Shapiro-Wilk normality test. Continuous variables were compared using ANOVA or Kruskal-Wallis tests (in case of non-normal distributions or violations in the assumption of homoscedasticity evaluated using Bartlett's test), followed by post-hoc comparisons between groups (corrected for multiple comparisons using Dunn's multiple comparison test). Correlation analyses between spectral power ratios and monthly number of headache or migraine days were performed using Spearman's rank correlation test corrected for multiple comparisons by applying a Bonferroni correction. Because alterations in the power spectrum of patients from the ictal migraine group are likely to be transient,^{1,39} these patients were not included in correlation analyses. The significance level for all tests was set at $P < .05$.

Results

There were no significant between-group differences in mean age or gender ratio in the whole subject sample, nor between disease duration among migraine subgroups (Table 1).

The results of spectral analyses are displayed in Table 2. Mean low-frequency (theta-alpha-low beta) power was significantly higher in headache-free episodic migraine patients compared to healthy controls (Kruskal-Wallis test $H = 8.330$, $P = .040$; Dunn's multiple comparisons test (episodic migraine patients vs healthy controls) $P = .030$, adjusted for multiple comparisons). Conversely, gamma power was higher in both ictal and chronic migraine patients (Kruskal-Wallis test $H = 14.00$, $P < .003$; Dunn's multiple comparisons tests: chronic migraine vs healthy controls, $P = .023$; ictal migraine vs healthy controls, $P = .013$, both adjusted for multiple comparisons) (Fig. 1 and 2). The low-frequency-to-gamma activity ratio was significantly smaller in ictal and chronic migraine patients compared to headache-free episodic migraine patients, and in ictal migraine patients compared to healthy controls (Kruskal-Wallis test $H = 16.33$, $P = .001$; Dunn's multiple comparisons tests: episodic vs chronic, $P = .032$; episodic versus ictal, $P = .012$; HV versus ictal, $P = .024$ (all adjusted for multiple comparisons). A similar trend was observed between chronic migraine patients and healthy controls, but it did not reach statistical significance ($P = .055$) (Fig 2). The low-frequency-to-gamma activity ratio was negatively correlated with the total number of monthly headache days ($\rho = -0.34$; $P = .015$), but not with the total number of migraine specific days ($\rho = -0.25$; $P = .08$) (Fig 3). A partial correlation (controlling for age) between the low-frequency/gamma activity ratio and the monthly headache days was also significant ($r = -.33$; $P = .02$). The N1-P1 amplitude of the

Table 2. Alpha and Gamma Power ($\times 10^2 \mu V^2/Hz$) and Their Ratio in the 4 Subject Groups

	HV		EM		CM		IM	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
Low frequency	635.6	± 12.1	651.0*	± 27.5	643.4	± 27.4	638.7	± 21.0
Gamma	881.9	± 62.7	901.9	± 53.4	976.6*	± 116.6	965.7*	± 91.2
Ratio	0.72	± 0.05	0.72	± 0.04	0.67†	± 0.08	0.67*†	± 0.06

Abbreviations: HV, healthy volunteers (n=20); EM, interictal episodic migraineurs (n=30); CM, chronic migraineurs (n=20); IM, ictal episodic migraineurs (n=20). $P < 0.05$ corrected for multiple comparisons, (*) as compared to controls, (†) as compared to interictal episodic migraine patients.

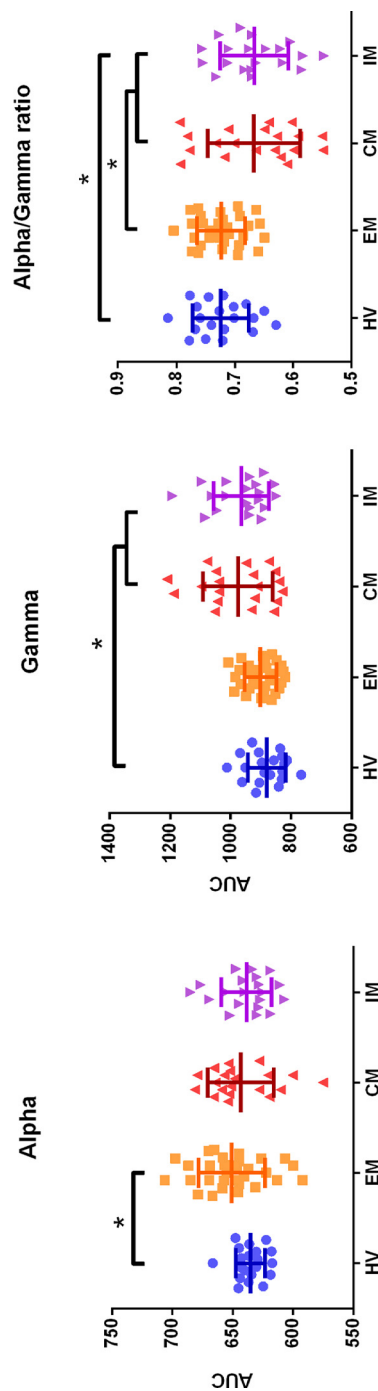


Figure 2. Pattern-reversal visual evoked potential spectral analyses showing Alpha (left) and Gamma (middle) and Alpha/Gamma area under the curve ratio (right) by subject group. Asterisks (*) indicate significant differences between groups ($P < .05$ corrected for multiple comparisons). Abbreviation: HV, healthy volunteers; EM, episodic migraine patients; CM, chronic migraineurs; IM, episodic migraineurs during an attack.

broad-band VEP was not significantly different between the groups (healthy controls: $5.088 \mu V \pm 1.444$; headache-free migraine patients: $5.860 \mu V \pm 2.361$; chronic migraine patients: $5.368 \mu V \pm 2.281$; ictal migraine patients: $6.396 \mu V \pm 2.436$; (one-way ANOVA $F_{(3,86)} = 1.399$; $P = .249$). Supplementary event-related spectral perturbations analysis (Fig 4) showed that gamma activity exhibited temporal fluctuations, as one would expect from a neural signal, rather than being constant over time, as would be 50 Hz power line noise or other possible sources of signal contamination.

Discussion

We measured power of low (theta/alpha/low-beta) and high (gamma) frequency oscillations embedded in pattern-reversal-VEPs (PR-VEP) in healthy controls, episodic migraine patients during or in between attacks, and chronic migraineurs. The results show that, during headache, gamma power is greater in patients than in healthy subjects. By contrast, in the absence of headache, episodic migraine patients have increased low-frequency power (theta/alpha/low beta). Concordantly, the low-frequency-to-gamma activity ratio was significantly higher in headache-free patients than during a migraine attack or in chronic migraineurs and negatively correlated with the monthly number of headache days.

We have previously found a decreased habituation of late visual induced gamma components in headache-free interictal episodic migraine patients.⁷ In the present study we focused on total gamma power and its relation with the low-frequency power spectrum analyzed in the frequency-domain, which is better suited to evaluate high-frequency oscillations. There is strong evidence showing that feedforward (afferent) volleys coming from the lateral geniculate nucleus induce oscillations within the gamma frequency range in the primary visual cortex (Fig 5). This frequency range has been associated with the efficiency of stimulus processing by thalamocortical networks^{15,36,40} and with the translation of the stimulus features into coherent perception (for a review, see Gray and Singer, 1995⁴²; Tallon-Baudry and Bertrand, 1999⁴⁴). Therefore, increased visually induced gamma (feedforward) activity during migraine attacks and in chronic migraine may reflect augmented efficiency in the thalamocortical circuit. This is in line with previous electrophysiological,^{8,9,23,43} and functional neuroimaging¹¹ studies showing that thalamocortical network activity is decreased in migraineurs during the headache-free interval, but increased during an attack and with migraine chronification.

On the other hand, it is known that pain is accompanied by widespread enhancement of gamma activity in the brain (prefrontal, midcingulate, and primary somatosensory cortices and insula)¹⁹ associated with contralateral alpha power reductions,³² which suggests that the former reflects tonic pain processing while the latter may be related to a top-down cognitive process linked to attention.^{4,5,17,18,45} Reciprocal anatomical and

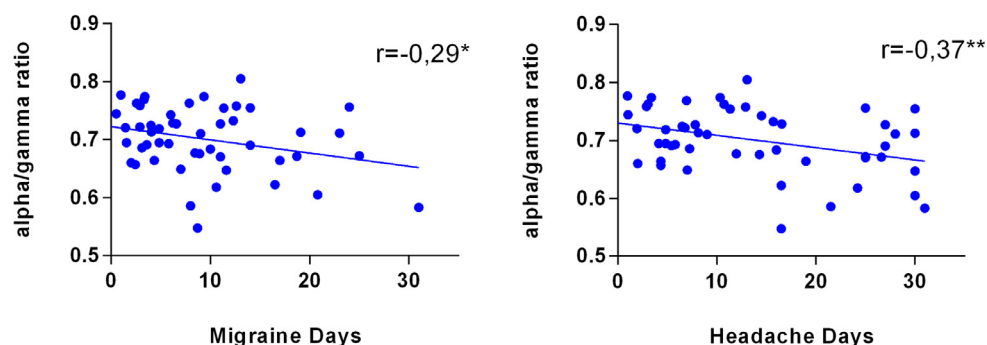


Figure 3. Correlation between the visually induced alpha/gamma power ratio and the monthly number of migraine days (left) or nonspecific headache days (right). (*) $P < .05$. Ictal migraine patients were not included in this analysis.

functional connections between the visual and the trigeminal systems are well documented in animals and human beings.^{3,25,31,37} In particular, convergence of nociceptive trigeminal and visual afferents in the posterior thalamus³⁰ may explain how head pain can amplify visually induced thalamocortical activity, and thus gamma power in PR-VEP.

As opposed to feedforward afferent activity that generates gamma oscillations in the primary visual cortex, feedback volleys from higher order visual areas (V2-V4)

induce oscillatory activity within the theta/alpha/low beta frequency range (Fig 5) that notably plays a role in focusing attention to salient unattended stimuli.^{24,28} Such feedback volleys reaching the visual cortex are able to modulate the response to visual afferents^{14,21,23} by selectively inhibiting high frequency (gamma) feedforward oscillations, and thus to exert a possible "gating" process.²² The sensory processing profile of migraine patients makes them vulnerable to sensory overload,^{2,16} and therefore, in need of compensatory

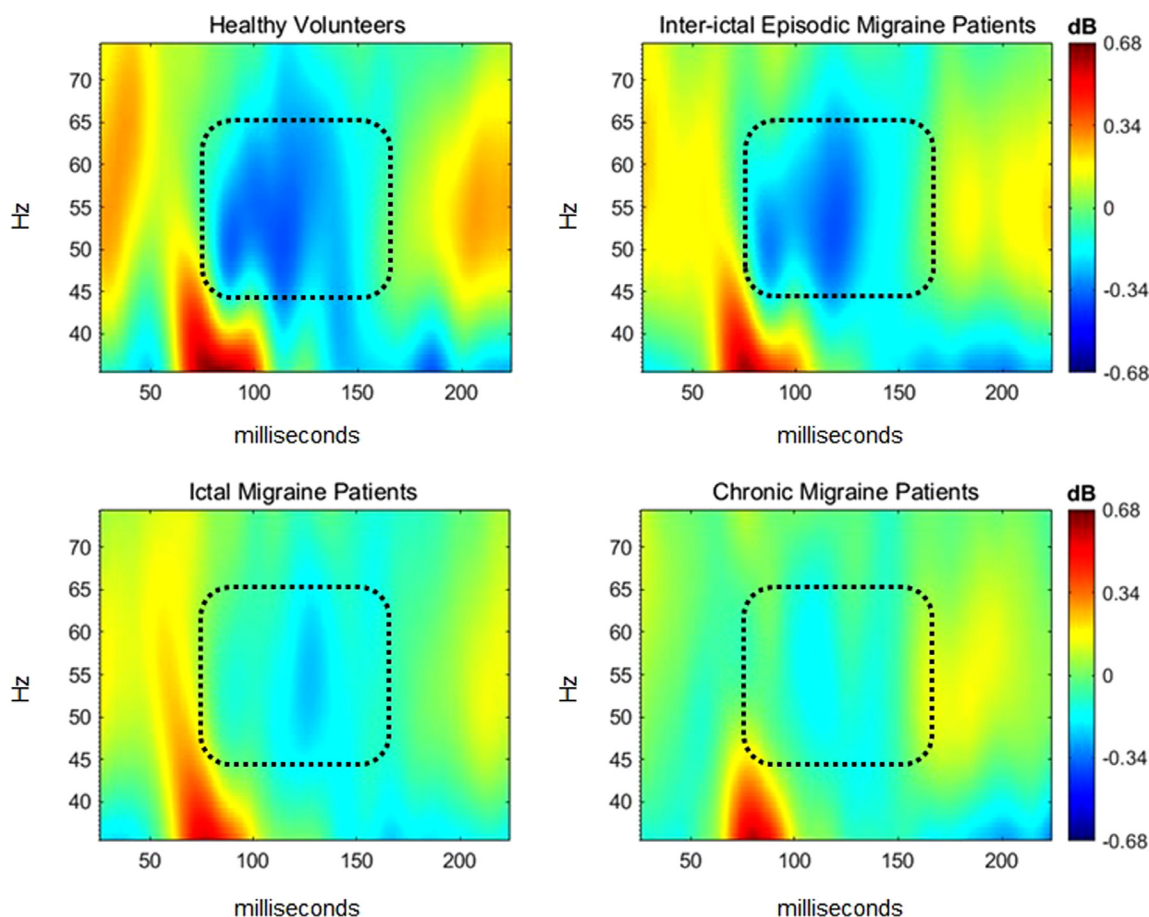


Figure 4. Event related spectral perturbations in the gamma frequency range. Gamma activity is dynamically modulated throughout time. Areas delimited by a discontinuous line show the time and frequency range where gamma suppression reaches its maximum in healthy controls and episodic migraine patients in the interictal period. See color-scale on the right. (Color version available online.)

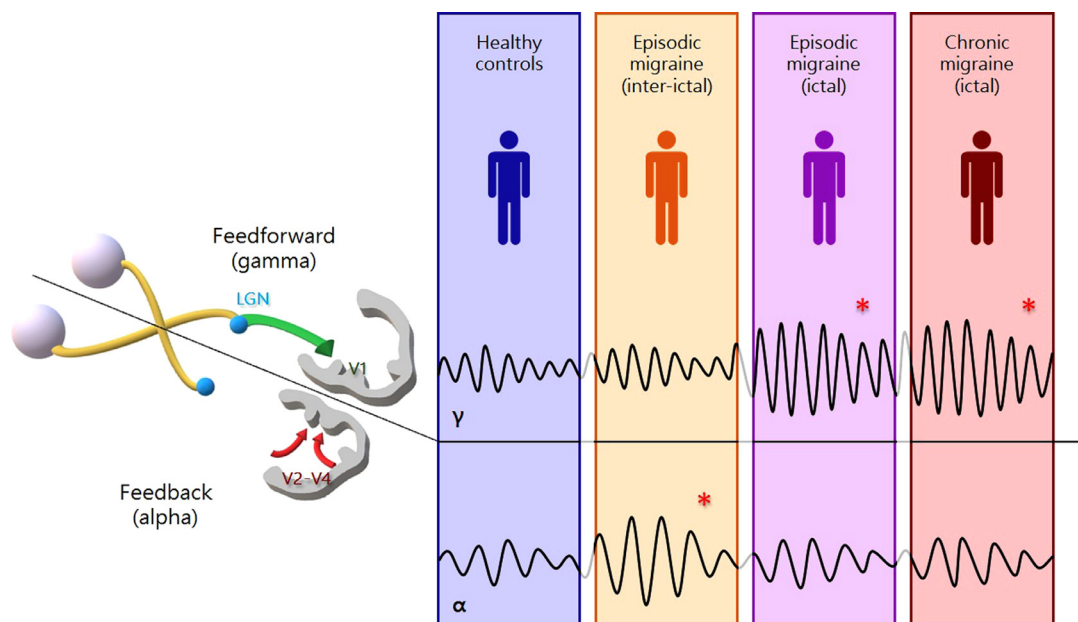


Figure 5. Schematic representation of feedback and feedforward signalling toward the primary visual cortex. Feedforward (green) signals reaching the primary visual cortex from the lateral geniculate nucleus induce oscillations in the gamma band frequency range. Feedback signals (red) originating in higher order visual areas (V2-V4) induce activity in the primary visual cortex within the alpha frequency band. Asterisks denote statistically significant differences. (Color version available online.)

protective mechanisms. Between attacks, repetitive photic stimulation causes whole-brain alpha hypersynchronization,⁴⁶ indicative of a diffuse cortical deactivation,³³ which may be favoured by the lower interictal activity in thalamocortical networks.⁸ Our finding of increased theta/alpha/low beta power during the interictal phase of episodic migraine may thus reflect an increased feedback inhibition restraining thalamocortical feedforward afferents as a protective (or compensatory) mechanism. Concordantly, short-range lateral inhibition in the visual cortex of episodic migraineurs was found increased at the beginning of a sustained visual stimulation, but decreased with subsequent persistent stimulus presentation.¹⁰ This phenomenon likely contributes to the lack of habituation of broad-band PR-VEP, and supports the hypothesis that the protective mechanism against sensory overload in migraine patients may at some point become overtaken.

The ratio between low frequency and gamma power was negatively correlated with disease activity, but more so with headache days than with qualified migraine days. Its lower value in chronic migraineurs could be due to the higher frequency of headache days in these patients rendering them more likely to be recorded in close temporal relation to an attack. The pathophysiological distinction between archetypal migraine attacks and episodes of mild headache that co-occur in migraine patients is a matter of debate. Clinical studies have shown that these mild headaches with a tension-type like phenotype respond just like full-blown migraine attacks to specific antimigraine drugs like triptans.²⁶ Our findings might suggest that most headaches in migraine patients, with or without migrainous features, have a similar pathophysiological underpinning. This hypothesis merits further studies

because of its potential implications in the diagnosis of chronic migraine.⁴⁹ Interestingly, the feedback/feedforward ratio was remarkably similar between ictal episodic and chronic migraine patients. Such similarity was also reported for other electrophysiological features⁶ and confirms that, chronic migraine resembles a "never-ending migraine attack" as far as cortical electrophysiology is concerned.³⁸

Our study has several limitations. Analysis of gamma band activity does not allow notch filtering at the frequency of the power line (AC) and one cannot exclude that the gamma band power was to some degree contaminated by the power line oscillations. However, as mentioned, gamma activity exhibited temporal fluctuations in our study, which would be expected from a neural signal, and was not constant over time, as would be 50 Hz power line noise. Also, artefact rejection with single channel recordings is restricted, and hence subtraction of muscle activity^{29,47} or miniature ocular saccades⁴⁸ was not possible. Moreover, the 2 standard deviations from the channel mean amplitude limit that we employed for artefact rejection was empirically chosen and, although apparently adequate, needs to be experimentally corroborated. Of note, since our analysis was limited to a single derivation (Oz), it lacks spatial resolution. Multichannel recordings using high-density EEG would allow to perform anatomical segregation of neural activity and much better artefact suppression. Analysing prestimulus spectral power, and the influence of different temporal frequencies of the visual stimulus would also be worthwhile. Likewise, although signal analyses were automated, blinding the investigators would have been advantageous. With regards to subjects, different patients were included in the ictal and interictal episodic migraine

groups. In future studies, it would be preferable to compare the same patients in and outside of an attack, which would allow a more powerful paired analysis. For some episodic migraine patients, the next attack following the VEP recordings occurred after the 30-day headache diary registry had ended and thus we were unable to correlate their electrophysiological results with time elapsed before/after the most proximal attack. Given that our sample of migraine patients was entirely composed of migraine

without aura patients, the results cannot be readily extrapolated to migraine with aura patients before further testing. Photophobia was not quantitatively assessed, which impeded us from correlating this clinical symptom with electrophysiological data. Finally, in the future it would be of interest to explore the dynamic, intraindividual fluctuations of the low frequency-to-gamma ratio over the migraine cycle, and its correlation with PR-VEP habituation, the most common neurophysiological abnormality in migraine.

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