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Visually evoked phase synchronization changes of alpha rhythm in migraine: Correlations with clinical features

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Abstract

Objective: This study aimed to compute phase synchronization of the alpha band from a multichannel electroencephalogram (EEG) recorded under repetitive flash stimulation from migraine patients without aura. This allowed examination of ongoing EEG activity during visual stimulation in the pain-free phase of migraine.
Methods: Flash stimuli at frequencies of 3, 6, 9, 12, 15, 18, 21, 24, and 27 Hz were delivered to 15 migraine patients without aura and 15 controls, with the EEG recorded from 18 scalp electrodes, referred to the linked earlobes. The EEG signals were filtered in the alpha (7.5−13 Hz) band. For all stimulus frequencies that we evaluated, the phase synchronization index was based on the Hilbert transformation.
Results: Phase synchronization separated the patients and controls for the 9, 24 and 27 Hz stimulus frequencies; hyper phase synchronization was observed in patients, whereas healthy subjects were characterized by a reduced phase synchronization. These differences were found in all regions of the scalp.
Conclusions: During migraine, the brain synchronizes to the idling rhythm of the visual areas under certain photic stimulations; in normal subjects however, brain regions involved in the processing of sensory information demonstrate desynchronized activity. Hyper-synchronization of the alpha rhythm may suggest a state of cortical hypoexcitability during the interictal phase of migraine.
Significance: The employment of non-linear EEG analysis may identify subtle functional changes in the migraine brain.

Keywords: Alpha rhythm; Phase synchronization; Photic stimulation; Migraine

1. Introduction

Migraine is an incapacitating disorder of neurovascular origin. In spite of a wealth of research, many unresolved issues in the pathophysiology of migraine remain. Neurophysiological examination of the period between migraine attacks has indicated that abnormal cortical excitability predisposes the individual to attack onset (Welch, 2003). Studies of evoked potentials and transcranial magnetic stimulation disclosed abnormalities of cortical information processing and excitability in both types of migraine between attacks, but revealed some conflicting results regarding a condition of hyper or hypo-excitability of the visual cortex (Ambrosini et al., 2003). Both Aurora et al. (1998) and Brighina et al. (2002), using TMS over the

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occipital lobe, reported an abnormally high prevalence of magnetophosphenes in migraine with aura patients between attacks. By contrast, Afra et al. (1998) obtained rather opposing results using a similar methodology and a circular coil; the prevalence of phosphenes was significantly lower in MA patients than in controls.

In previous studies of visual evoked potentials in migraine, spectral fast Fourier analysis of the EEG during steady-state flash stimulation have shown that the fundamental F1 component (Nyrke et al., 1982; Genco et al., 1994; de Tommaso et al., 2003) and the alpha band (Simon et al., 1982) are more powerful in migraneurs than in healthy controls. These results concur with the pioneering finding of an increased photic driving of the EEG (Golla and Winter, 1959) in migraine patients, and suggest that sustained visual stimulation induces more synchronous net activity in the visual cortex of migraine patients between attacks.

When subjects are submitted to multimodal stimulations, several changes occur in ongoing EEG/MEG activity that signal activation of cortical regions. Increased cellular excitability in thalamo-cortical systems results in a low amplitude, desynchronized EEG (Steriade and Llinas, 1988). However, when patches of neurons display coherent activity in the alpha band, an active processing of information is very unlikely, and it may be assumed that the corresponding networks are deactivated (Pfurtscheller and Lopes da Silva, 1999). This would suggest that evaluation of the phase synchronization of the EEG rhythm during visual stimulation may help clarify whether there is increased or decreased visual cortex excitability in migraine patients during the non-symptomatic phase.

Phase synchronization, a concept introduced in the field of nonlinear dynamics (Rosenblum et al., 1996), provides a measure of synchronization that is an alternative to conventional linear approaches. The linear measure of correlation between two signals as a function of frequency (spectral coherence) may not be the optimal measure for the study of phase synchrony between different brain regions, as coherence has low utility when managing non-stationary data-sets, and rapid changes in coherence cannot be tracked. Recently, new methods, founded on the theory of nonlinear dynamical systems, have been proposed to overcome this limitation (Kantz and Schreiber, 1997).

In a preliminary study, we evaluated phase synchronization of alpha rhythm in a cohort of migraine without aura patients, and observed a clear tendency toward hypersynchronization of the alpha rhythm during photic stimulation at certain frequencies (Angelini et al., 2004). This finding may support a pattern of hypo-excitability of neuronal networks during photic stimulation in migraine patients. However, that study was primarily concerned with the methodological approach to EEG analysis, and did not examine any clinical aspects of migraine patients.

The aim of this study was to evaluate the state of cortical excitability during repetitive flash stimulation in non-symptomatic migraine by performing analysis of phase synchronization in the alpha band and correlating the synchronization pattern with the clinical features of migraine.

2. Methods

2.1. Subjects

The patient group consisted of 15 migraine patients without aura (eight male, seven female), diagnosed according to IHS criteria (International Headache Society Headache Classification Committee, 2004). The mean age was 39 years, with a range between 26 and 59 years. The mean disease history was 16.5 years (range: 1–40 years) with a mean attack frequency of 6.2 days per month with a headache's range between 1 and 16. All patients were diagnosed after a 6-month follow-up period. At the moment of examination patients were all in the interictal state, and the time from the end of the last attack was at least 72 h (mean: 110±21 h); the interval before the next headache was also verified from the headache diary during a subsequent clinical examination, thereby avoiding the inclusion of patients that experienced a migraine in the 48 h following the experimental task (mean 102±10.2 h). Fifteen healthy subjects (5 males, 10 females) with a mean age of 27.1 years (range: 24–34 years) served as a control group. The alpha peak frequencies, evaluated as described in Klimesch (1999), were 9.87±1.03 Hz for control subjects and 10.30±1.83 Hz for patients (Result of Wilkoxon test: $p=0.48$). All subjects had normal or corrected to normal vision, and no concomitant general, neurological or psychiatric disease; no patients had taken any psycho-active drug during the 6 months preceding the study; in the only case experiencing 16 days/month mean migraine frequency, the preventive treatment was avoided for a gradual reduction of attacks during the 6 months follow-up.

The research received prior ethics approval by our Department of Neurological and Psychiatric Sciences of Bari University; informed consent was obtained from each participant.

2.2. Stimuli

Flash stimuli with a luminous frequency of 0.2 J were used to elicit the SVEPs. Subjects were tested in a dimly lit room while seated in a comfortable chair. The distance to the stroboscope was 20 cm. For each stimulus frequency, the 40 s stimulus interval was followed by a 20 s rest period. The subjects were instructed to relax during the experiment and keep their eyes closed; to avoid drowsiness, subjects were asked to open their eyes for almost 10 s during the rest periods and converse with the experimenter, although EEG tracks recorded with eyes open were not used for the analysis. Stimulus frequencies were presented in a random order. In this experiment, we used frequencies of 3, 6, 9, 12, 15, 18, 21, 24 and 27 Hz.

2.3. Recording

EEG recordings were obtained using a MICROMED (Mogliano Veneto, Italy) System98 apparatus. Electrodes were positioned according to the international 10–20 system, at Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, C4, T4, T5, P3, Pz, P4, T6, O1 and O2. The reference electrode was positioned at the linked earlobes (A1+A2), with the ground electrode placed over the nasion. The EEG signals were sampled at a rate of 128 Hz, and filtered at 0.1–60 Hz. Eye movements were monitored by a pair of electrodes placed at the outer canthi of both eyes in order to show ocular artefacts: EEG tracks containing artefacts were rejected by visual inspection.

2.4. EEG analysis

For all stimulus frequencies, we evaluated the phase synchronization index proposed by Tass et al. (2003). Our approach was based on the Hilbert transformation. Instantaneous phases for a passband filtered signal $s(t)$ were estimated via an analytic signal $\xi(t)$, which is defined as a complex function of time:

$$\xi(t) = s(t) + jw(t) = A(t)e^{j\phi(t)}. \quad (1)$$

And where $w(t)$ is the Hilbert transformation of $s(t)$:

$$w(t) = \frac{1}{\pi}\text{P.V.}\int_{-\infty}^{\infty}\frac{s(\tau)}{t-\tau}\mathrm{d}\tau. \quad (2)$$

The notation P.V. denotes that the integral is used according to the Cauchy principal value. In practice, the transformation can be realized by a filter whose amplitude response is uniform, with a phase response that is a constant $\pi/2$ lag (Rosenblum et al., 1996). We used the specific MATLAB function that calculates the Fourier transformation of the signal and sets to zero those coefficients that correspond to negative frequencies, and applies the inverse transformation. To quantify the phase synchronization, the index formulated by Tass et al. (2003) was used. For all pairs of electrodes, the corresponding EEG signals were filtered in the alpha band and the instantaneous phases of the two selected channels $\varphi_1(t)$ and $\varphi_2(t)$ were evaluated as described above. The phase difference $\Delta\Phi(t)=[\varphi_1(t)-\varphi_2(t)]_{\text{mod } 2\pi}$ was then evaluated for all times, t. The interval $[0, 2\pi]$, where the phase difference is defined, was divided into K bins. Phase synchronization is characterized by the appearance of peaks in the distribution {n_k—relative frequency of phase differences in kth bin} and of $\Delta\Phi$ onto the K bins. By representing the entropy of the actual distribution of phase differences as:

$$S = -\sum_{k=1}^{K} n_k \log(n_k) \quad (3)$$

and naming $S_{\max}=\log(K)$ as the entropy of the uniform distribution, the synchronization index ρ is defined as follows:

$$\rho = \frac{S_{\max} - S}{S_{\max}}. \quad (4)$$

The index ρ is represented by values ranging from 0 to 1, where 1 represents the complete phase coupling. We also considered the linear measure of correlation, obtained by calculating the linear synchronization, as a function of the frequency. Further, we considered it as the normalized amplitude of the cross spectrum of the two time series (coherence function) (Otnes and Enochson, 1972) and integrated it into the band under consideration.

2.5. Statistics

EEG signals were filtered in the alpha band (8–12.5 Hz). The EEG signals were also filtered in the other EEG bands (theta 4–7.5 Hz, delta 1–3.5 Hz, beta 13–30 Hz). The phase synchronization index described above was evaluated for all pairs of electrodes, for all thirty subjects and for all frequencies of the flash stimuli. These indexes were subsequently averaged over all the possible pairs of sensors, for each subject, both in the presence of stimuli and in spontaneous conditions.

For each stimulation frequency, we then calculated the ratio

$$\Gamma = \log\left(\frac{\rho^{\text{flash}}}{\rho^{\text{spontaneous}}}\right), \quad (5)$$

where ρ^{flash} is the mean phase synchronization in presence of flash stimuli, and $\rho^{\text{spontaneous}}$ is the mean spontaneous phase synchronization. This ratio measures how phase synchronization varies, in the presence of the stimuli, with respect to basal conditions (i.e., the net effect of the stimulus). Our supervised analysis tested how much the index Γ separates the patients and the controls. For each of the nine frequencies, we applied the paired t-test to Γ values and evaluated the probability P_ω that the 30 Γ indexes, from patients and controls, were drawn from the same distribution. However, this approach to our data results in multiple comparisons. To control the number of false positives, we used the Bonferroni method.

A topographic analysis has also been performed, in order to check whether the phenomenon was localized in a particular cortical region. We evaluated, for each sensor s,

$$\Gamma_s = \frac{\rho_s^{\text{flash}}}{\rho_s^{\text{spontaneous}}} \quad (6)$$

where subscript s means averaging only over the pairs where s is one of the two sensors. For each stimulus frequency, we applied paired t-test to select, among the 18 electrodes, those separating the patients from controls, according to their Γ_s (3).

Table 1
The probabilities that the 30 Γ values of patients and controls were drawn from the same distribution, according to the paired t-test

3 Hz	6 Hz	9 Hz	12 Hz	15 Hz	18 Hz	21 Hz	24 Hz	27 Hz
0.0791	0.1030	0.0048	0.0451	0.0285	0.0521	0.0274	0.0051	0.0053

The frequencies are significant after Bonferroni correction are darkened.

The linear correlation between Γ and age, duration of illness and frequency of headache was performed.

3. Results

Filtering the signals, neither around the fundamental frequencies of flash stimulation, nor in the physiological EEG bands beta, theta and delta, led to significant differences in the measures of synchronization between patients and healthy subjects. On the other hand, as a control task, filtering the signal around 24 Hz, a significant increase of both coherence and phase synchronization between O1 and O2 was found in both patients (coherence: $p=0.0167$; index Γ: $p=0.0077$) and controls (coherence: $p=0.0128$; index Γ: $p=0.0046$) under 24 Hz flash stimulation, in comparison with the spontaneous condition. This pattern was not significantly different between patients and controls. When we considered the EEG filtered in the alpha range, our supervised analysis showed that the index Γ separated the patients and controls for the 9, 24 and 27 Hz stimulus frequencies. Table 1 describes the application of paired t-test, corrected by Bonferroni method to our data: the frequencies 9, 24 and 27 Hz separated patients from controls. The average Γ index, computed across all stimulating electrodes and derivations for all the stimulating frequencies, was also significantly different between patients and controls ($p=0.0144$).

For the 9, 24 and 27 Hz stimuli in particular, hyperphase synchronization was observed in patients, whereas healthy subjects were characterized by reduced phase synchronization (Fig. 1). In migraine patients, the phase shift in the presence of flickering between Fp1 and Fp2 was 0 across almost the whole interval; no such behaviour was observed in the spontaneous case (Fig. 2).

Results from the topographic analysis are described in Fig. 3, with the null hypothesis probabilities shown for all sensors and each frequency. At 9 Hz, 24 Hz and 27 Hz stimulus frequencies, most electrodes separated patients from controls (Fig. 3).

The linear index of synchronization (based on spectral coherence) did not lead to any separation between patients and controls: for example, in Table 2, we report the t-test probabilities obtained for the 9 and 24 Hz stimuli.

We evaluated the linear correlation between Γ and age in the whole group of patients and controls, finding no significant correlation (Fig. 4). Analogously, for patients, no significant correlation was found with the duration of pathology and frequency of migraine attacks (Fig. 4).

4. Discussion

Our data show that for patients, the mean phase synchronization of the alpha rhythm increases in the presence of visual stimuli, whereas it decreases in controls,

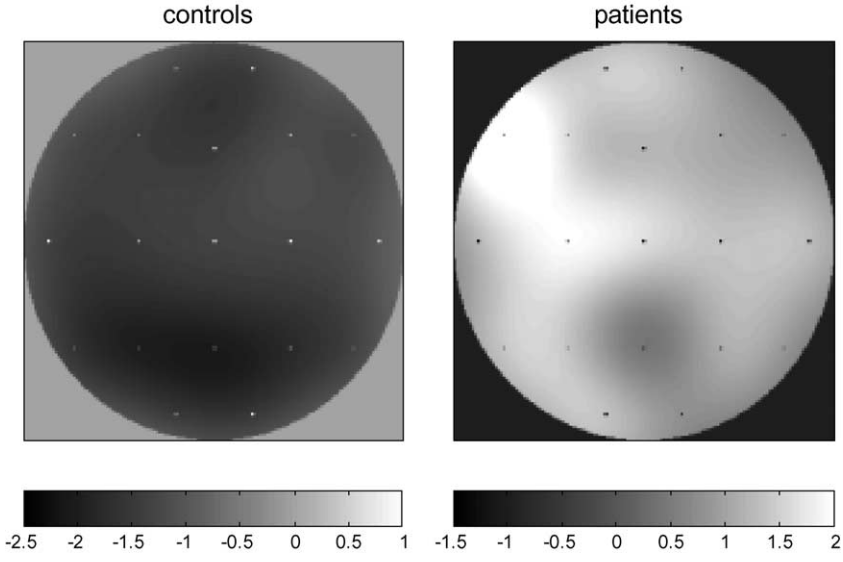

Fig. 1. In the case of the 24 Hz stimulus, the mean Γ_s (for patients and controls) is represented for all 18 electrodes. On average, phase synchronization increases for patients (p less than 0.00001) and decreases for controls (p less than 0.00001).

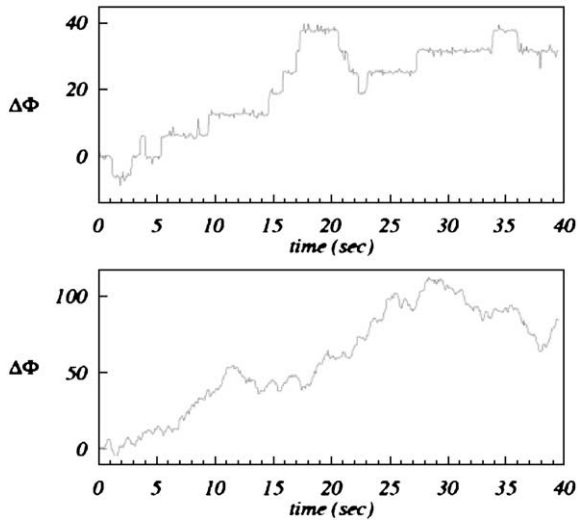

Fig. 2. Time evolution of $\Delta\Phi$ for the pair Fp1–Fp2 in a female migraine patient, 32 years old. Similar patterns are found for the other patients and other pairs of electrodes. Top: with 9 Hz stimulation. Horizontal segments, several seconds long, are visible and correspond to zero phase delay between signals from the two electrodes. Bottom: without stimulation. No horizontal segment is observed.

Table 2
Values of p for spectral coherency, alpha band

	9 Hz	24 Hz
F1	6.07e−01	5.41e−01
F2	8.03e−01	7.15e−01
F7	4.49e−01	3.48E−01
F3	7.77e−01	9.42e−01
FZ	6.01e−01	9.78e−01
F4	7.96e−01	4.61e−01
F8	6.83e−01	7.01E−01
T3	6.18e−01	6.90e−01
C3	2.60e−01	7.54e−01
C4	2.09e−01	6.97e−01
T4	5.71e−01	5.84e−01
T5	8.91e−01	9.39e−01
P3	6.48e−01	7.82e−01
PZ	3.25e−01	8.42e−01
P4	2.75e−01	9.97e−01
T6	5.65e−01	7.86e−01
O1	7.19e−01	9.86e−01
O2	5.79e−01	9.81e−01

Probabilities that Γ_s values are drawn from the same distribution, evaluated using the spectral coherence measure of synchronization. Values are displayed for all sensors and for the 9 and 24 Hz stimulation.

confirming previous results (Angelini et al., 2004). This pattern was similar for 9, 24 and 27 Hz stimulation, and a trend toward a different alpha rhythm synchronization behaviour was found for the most of the stimulating frequencies. Since separating electrodes from all regions of the cortex (frontal, parietal, central, temporal and occipital) have been found, it follows that the phenomenon described here is extended over the entire cortex, rather than localized to a limited region.

The classical measure of synchronization, based on spectral coherence, was not able to explain this phenom-

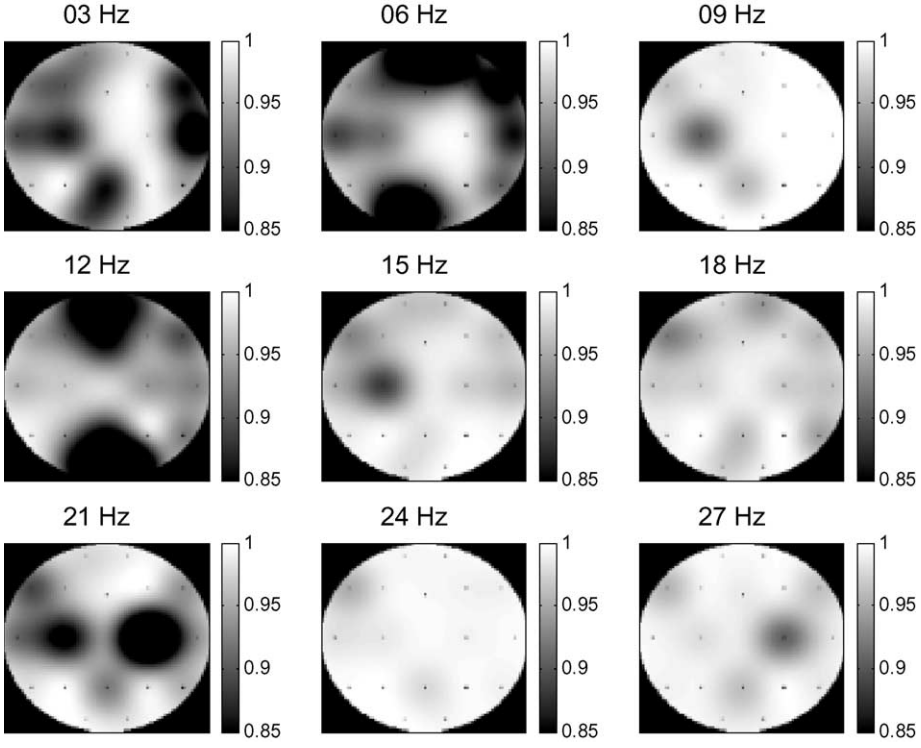

Fig. 3. Probabilities that Γ_s values are drawn from the same distribution, evaluated according to the paired t-test, displayed for all sensors and all stimulation frequencies. In the maps, $1-p$ value was represented: lighter grey corresponds to separating electrodes. For stimulation at 9-24-27 Hz, all electrodes were found to separate significantly the two groups, except for F7, C3, Pz (for 9 Hz), F7, T3, C3, Pz (24 Hz), F7, F8, Pz, C4 (27 Hz).

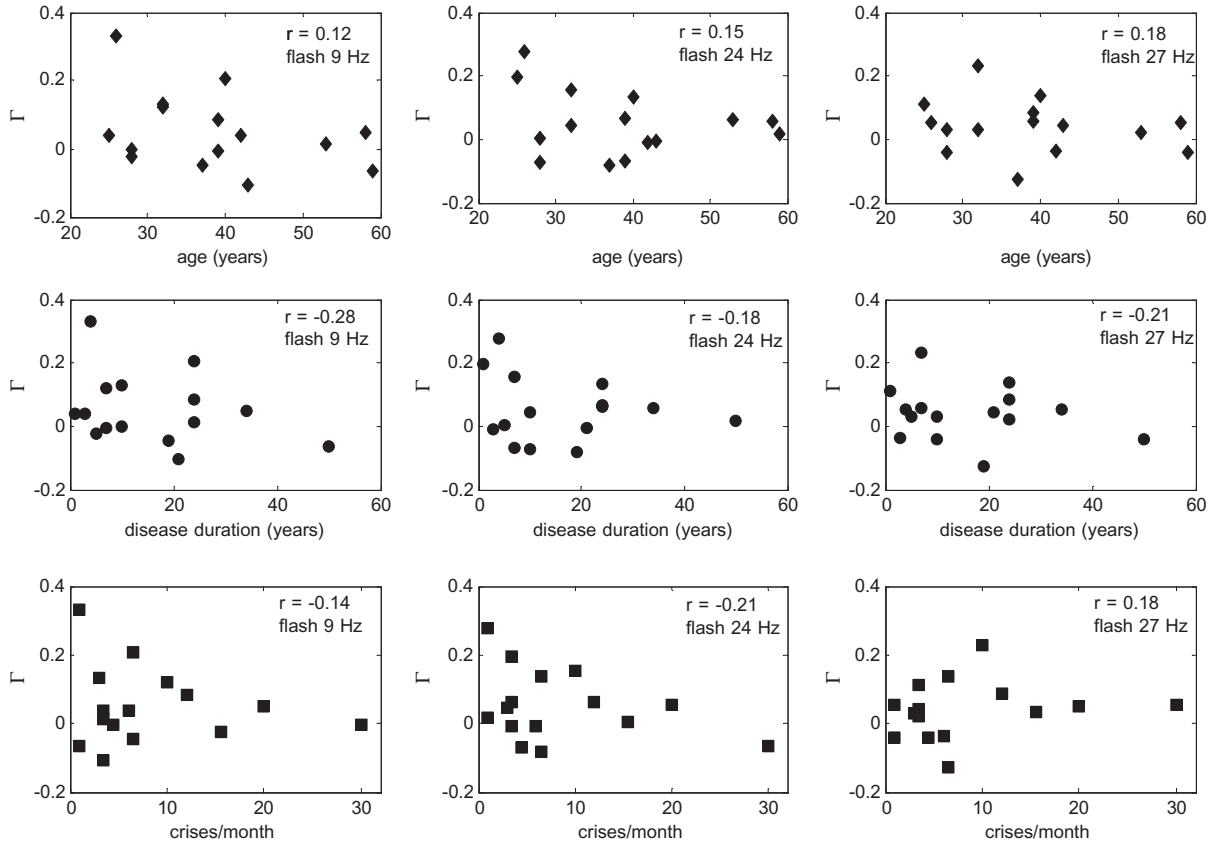

Fig. 4. Correlations between the main clinical feature and alpha phase synchronization (Γ). For the age, the Pearson correlation test was computed considering patients and controls ($n=30$), with a 5% probability critical value of 0.361; for the duration of illness and frequency of migraine, the 5% probability critical value was 0.514 ($n=15$).

enon. The current failure of this method to reveal hyper-synchronization can be explained by the fact that alpha waves are oscillatory and non-stationary signals: the technique of analytic signals is the suitable tool for these conditions (Quiroga et al., 2002).

A fundamental issue in the characterization of brain function is the understanding of functional coordination between brain regions. Whilst it is comprehensible that 9 Hz stimuli might cause hyper-synchronization in the alpha band (8–12.5 Hz), an explanation is required to understand how 24–27 Hz stimuli may act on alpha oscillations. As the brain is a nonlinear dynamical system, and sub-harmonics of 24–27 Hz fall in the alpha band, stimulation in the 24–27 band may cause hyper-synchronization of the alpha rhythm through their sub-harmonics. Additionally, 18 Hz stimulation was very close to separating the groups, and a similar trend was observed for 12, 15 and 21 Hz stimulation (see Fig. 3 and Table 1). The stimulating frequencies causing synchronization of the alpha rhythm did not cause a separating pattern of synchronization between patients and controls when the signal was filtered around their entire spectral band. Accordingly, their phase synchronization results should not be linked exclusively with their alpha-band-filtered sub harmonics. In addition, the average Γ index revealed a generalized pattern of alpha rhythm synchronization under all the frequencies of stimulation in migraine patients, so the alpha rhythm synchronization may be a generalized effect of repetitive visual stimulation. In contrast with the results obtained in migraine, normal subjects exhibited desynchronization of the alpha rhythm during visual stimulation, an effect that was previously described and associated with the mechanisms of sensory information processing (Lopes da Silva, 1991). Alpha desynchronization signals the transition between a cortical resting (idling) state with low-frequency rhythms and an activated state where higher frequencies occur (Klimesch, 1996; Pfurtscheller and Lopes da Silva, 1999); the blocking of the oscillatory activity in the alpha band would subserve a thalamo-cortical or cortico-cortical gating function (Lopes da Silva, 1991; Thut et al., 2003). In migraine patients, the cooperative or synchronized behaviour of a large number of neurons was shown by coherent activity in the alpha band during the visual stimulation. In this condition, an active processing of information is very unlikely and it may be assumed that the corresponding networks are inactive (Pfurtscheller and Lopes da Silva, 1999). We can hypothesize that the migraine brain shows a persisting idling rhythm of the visual areas, extended over the entire cortex, suggesting a diffuse cortical inactivation under certain photic stimulations, while in normal subjects the block of

oscillatory alpha rhythm signals the processing of visual sensory information (Pfurtscheller, 1992). In normal subjects, application of low-frequency repetitive TMS over the occipital pole to reduce cortical excitability resulted in a reduction of the alpha rhythm desynchronization caused by visual stimulation: accordingly, the pattern of synchronization of the alpha rhythm may be considered a sign of cortical hypoexcitability (Thut et al., 2003). The pattern of enhanced alpha synchronization after photic stimulation seemed quite independent from the main clinical features: it was not correlated with age in patients and controls, showing that the slight age difference between the two groups should not influence the alpha pattern, linked with migraine disease itself. In addition, we know that dramatic changes of evoked cortical responses, and thus of cortical excitability, occur 24 h before and during the migraine attack (de Tommaso et al., 1998; Judit et al., 2000). We failed however to observe any correlation between the degree of alpha rhythm synchronization and the time from the last attack, because the recording from each patient occurred at a time with a significant period from the last and the next attack. The alpha band synchronization under certain frequencies may thus be considered an inter-ictal pattern, probably intrinsic to migraine and predisposing to the attack. In this view, the migraine brain appears in a state of cortical hypoactivity during visual stimulation: this finding would confirm the most recent opinion of the neurophysiological features of migraine, dealing with a decreased level of cortical preactivation to sensory stimulation (Schoenen et al., 2003). Previously, migraine patients showed enhanced visual reactivity to the 24−27 Hz frequencies (de Tommaso et al., 1999), which in the present study caused a clear alpha band synchronization, without a pattern of enhanced synchronization in their fundamental bands: the synchronization of the ongoing EEG alpha activity over almost the entire scalp may be a compensatory phenomenon, aiming to reduce the effect of the luminous stimuli, or alternatively, a state of cortical hypoactivity, with a reduced processing of visual sensory information favouring an aberrant response to repetitive flash stimulation.

Taken together, the results of the study confirm that the employment of non-linear EEG analysis may outline subtle functional changes in the migraine brain: it is characterized by an aberrant reactivity to environmental, and specifically, visual stimuli, which cause abnormal cortical excitability during the pain-free phase, with a reduction of the cortical processes of sensory information elaboration. It has to be defined whether this state changes during the attack, in relation to the decrease of visual reactivity (de Tommaso et al., 1998), confirming that the alternating of migraine and non-migraine phases corresponds to a homeostatic mechanism, aiming to normalize the state of abnormal cortical excitability. Another crucial aspect of this question regards the possible subtle cognitive changes linked with the abnormal cortical information processing during sensory stimulation.

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