Steady-state visual evoked potentials and phase synchronization in migraine

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We investigate phase synchronization in EEG recordings from migraine patients. We use the analytic signal technique, based on the Hilbert transform, and find that migraine brains are characterized by enhanced alpha band phase synchronization in presence of visual stimuli. Our findings show that migraine patients have an overactive regulatory mechanism that renders them more sensitive to external stimuli.

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Phase synchronization was introduced for coupled chaotic systems by Rosenblum et al. [1] and has been confirmed experimentally [2]. This concept, introduced in the field of nonlinear dynamics, provides a measure of synchronization alternative to conventional linear approaches. It may be useful for biological time series, in particular to the study of electroencephalographic (EEG) signals, where synchronization phenomena are expected to play a major role for establishing the communication between different regions of the brain [3].

Migraine is an incapacitating disorder of neurovascular origin, which consists of attacks of headache, accompanied by autonomic and possibly neurological symptoms. It is estimated that in the USA, 5% of the general population suffer at least 18 days of migraine a year, and more than 1% have at least one day of migraine a week [4]. In spite of a lot of research, there are still many unresolved issues in the pathophysiology of migraine. There is a tendency to believe that migraine starts with an underlying central nervous system disorder, which, when triggered by various stimuli, sets off a chain of neurologic and biochemical events, some of which subsequently affect the brain’s vascular system. No experimental model fully explains the migraine process [5]. A wide range of events and conditions can alter conditions in the brain that bring on nerve excitation and trigger migraines. They include emotional stress, intense physical exertion, abrupt weather changes, flickering lights, and many others. The question we address here is: how does the response of migraine patients to such events differs from those of healthy persons? To address this problem, we investigate synchronization phenomena in Electroencephalograms (EEGs) recorded from migraine patients in presence of repetitive visual stimuli (steady-state visual evoked potentials, SVEPs [6]), and study how synchronization between different brain regions varies in presence of external stimuli (i.e., while brain is processing external information). We find that migraine brains show increased alpha band phase synchronization, while healthy persons show a decreased one. Our results suggest that migraine patients have an overactive regulatory mecha-
nism, prone to instability, which renders them more sensitive to environmental factors.

Our data are as follows. EEG is recorded from fifteen patients affected by migraine without aura, in presence of visual stimuli. During the acquisition, flash stimuli are presented to the subjects repetitively at a rate of 3-6-9-12-15-18-21-24-27 Hz. The mean age of patients is 38.7 years (range 24-48 years). Each frequency of stimulation is delivered by a flash settled at a luminance of 0.2 joules for at least 20 seconds; an interval of 20 seconds is interposed between the different trains of stimulation. EEG data are recorded by 18 scalp electrodes, placed according to the International 10-20 system, referred to CZ derivation. Impedance is settled below 5 KΩ. EEG is digitally filtered off line by means of a digital filter with a band-pass of 0.3-30 Hz; the sampling rate is 128 Hz. Examples of EEG signals are shown in fig. 1 also spontaneous EEG (i.e. in the absence of stimuli) is recorded for all patients, see fig. 2. All patients are in the inter-ictal state, the time from the end of the last attack being at least 72 hours. Moreover, EEG data from fifteen healthy subjects (ages ranging from 22 to 45 years) are measured so as to have a control group.

We recall how to detect $n : m$ phase synchronization in noisy scalar signals. Based on general theorems on analytical functions the following relation holds

$$\text{Im } \zeta(t) = \frac{1}{\pi} P.V. \int_{-\infty}^{+\infty} \text{Re } \zeta(\tau) \frac{d\tau}{t - \tau}. \quad (1)$$

This equation is known as the Hilbert transform and it is used to form, starting from a signal $s(t) = \text{Re } \zeta(t)$, the analytic signal $\zeta(t) = A(t) e^{i \phi(t)}$, where $A(t) = \sqrt{s^2(t) + \tilde{s}^2(t)}$, and $\tilde{s}(t) = \text{Im } \zeta(t)$. To control the possible synchronization of two signals $s_1(t), s_2(t)$ the following procedure is applied: the instantaneous phases $\phi_1(t)$ and $\phi_2(t)$ are computed and the so called generalized phase differences

$$\Phi_{n,m}(t) = |n \phi_1(t) - m \phi_2(t)|_{\text{mod}2\pi}, \quad (2)$$

with $n, m$ integers, are evaluated. Phase synchronization is characterized by the appearance of peaks in the distribution of $\Phi_{n,m}$ and quantified by comparing the actual distribution with a uniform one in the following way. The $n : m$ synchronization index of $s_1$ and $s_2$ is defined as $\rho_{n,m} = \frac{|S_{\text{max}} - S_{n,m}|}{S_{\text{max}}}$, where $S_{n,m}$ is the Shannon entropy of the distribution of $\Phi_{n,m}$ and $S_{\text{max}}$ is the entropy of the uniform distribution; in the case at hand only $1 : 1$ synchronization leads to interesting results.

Let us now turn to describe our findings. The EEG signals are filtered in the alpha band (8-12.5 Hz) and the synchronization index above described is evaluated for all pairs of electrodes, for all thirty subjects and for all frequencies of the flash stimuli. These indexes are subsequently averaged over all the possible pairs of sensors, for each subject both in presence of stimuli and in spontaneous conditions. These mean values do not separate patients from healthy subjects; what emerges as correlated with the migraine pathology is the ratio $\gamma = \rho_{1,1}^f / \rho_{1,1}^{sp}$, where $\rho_{1,1}^f$ is the mean phase synchronization in presence of flash stimuli, whereas $\rho_{1,1}^{sp}$ 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 neat effect of the stimulus. Our supervised analysis (hypothesis testing) shows that the index $\Gamma = \ln (\gamma)$ separates the class of patients and the class of controls for stimulus frequencies of 9,24,27 Hz. For each of the 9 flash stimuli frequencies $\omega$, we apply the paired t-test to evaluate the probability $P_\omega$ that indexes $\Gamma$s were drawn from the same distribution (the null hypothesis); in seven cases out of nine this probability is less than 0.05, the standard value used in literature to reject the null hypothesis. However, here we deal with multiple comparisons. To control the number of false positives, we use the false discov-
ery rate (FDR) method. This procedure selects the stimuli frequencies 9-24-27 Hz as separating patients from controls (see fig.4), with the expected fraction of false positive 0.05. The same frequencies (9-24-27 Hz) are selected by use of the standard Bonferroni correction for multiple comparisons as well as by FDR if probabilities are evaluated by the non-parametric Wilcoxon rank sum test (see fig.3).

A topographic analysis is also performed, in order to check whether this phenomenon is localized in some cortex region. We evaluate, for each sensor \( s \), \( \Gamma_s = \ln((\langle \rho^{T,11}_s \rangle)/\langle \rho^{o,11}_s \rangle) \), where \( \langle \cdot \rangle_s \) means averaging only over the pairs where \( s \) is one of the two sensors. For each frequency of stimuli, we apply FDR method to select, among the eighteen electrodes, those separating patients from controls according to their \( \Gamma_s \). The results are depicted in Figures 3: (9 Hz case) and 4: (24 Hz): eleven electrodes are recognized as separating in the case of 9 Hz stimuli and thirteen in the case of 24 Hz; no electrode is found to be individually separating when 27 Hz stimuli are considered. Since separating electrodes from all the regions of the cortex (frontal, parietal, central, temporal and occipital) are found, it follows that the phenomenon here described is extended over all the cortex, not being localized in a limited region. Its diffuse nature suggests that genuine spatial synchronization is here involved; indeed, volume conduction effects would induce spatially more localized change.

Our data show that, for patients, the mean phase synchronization increases in presence of visual stimuli, whereas it decreases in controls. For example, in the case of 24 Hz stimuli, and for all the sensors, the mean value (over subjects) of \( \Gamma_s \) is shown in fig. 4: hyper phase synchronization is observed in patients, whereas healthy subjects show a reduced phase synchronization. Similar patterns occur for 9 and 27 Hz stimuli. In fig. 5 the histograms of \( \Phi_{1,1} \), corresponding to electrodes T3 and T5, are shown for a migraine patient and for a control, both under stimulation and spontaneously. The distribution, when stimuli are delivered, broadens for the healthy person while becoming more peaked for the patient. This behavior is further illustrated in fig.6 where the time evolution of the phase difference between two sensors is depicted for a migraine patient, both subject to stimuli and in spontaneous conditions. In presence of flash phase locking, in the two signals, is observed for time segments several seconds long; no such locking is observed in the spontaneous case. Phase difference curves, for a control, are drawn in fig.7. It is worth stressing that this phenomenon is not mined if coherence is used to measure synchronization: considering the linear index obtained by integration of the coherence function (normalized amplitude of the cross spectrum of the two time series) in the alpha band, the corresponding \( \Gamma \) and \( \Gamma_s \) quantities do not lead to separation between patients and controls for any frequency of stimulation. We show that migraineurs are characterized by alpha band hyper-synchronization in presence of visual stimuli. We also show how this varies with the frequency of the flash, and present a topographic analysis where separating electrodes are recognized. Whilst it is comprehensible that 9 Hz stimuli might cause hyper-synchronization in the alpha band (8-12.5 Hz), in order to figure how 24-27 Hz stimuli may act on alpha oscillations we observe that brain is a nonlinear system, and sub-harmonics of 24-27 Hz fall in the alpha band: stimulation in the 24-27 band may cause hyper-synchronization through their sub-harmonics. However a similar behavior is not observed for other frequencies with sub-harmonics in the alpha band, like 18 Hz: further investigation is needed to clarify this aspect of the phenomenon. It will be also interesting to investigate the

![FIG. 4: In the case of 24 Hz stimuli, the mean of \( \Gamma_s \) (over patients and over controls) is represented for all the eighteen electrodes. On the average, phase synchronization increases for patients and decreases for controls.](image)

![FIG. 5: Histogram of \( \Phi_{1,1} \) for the pair T3-T5. (a) A healthy person without stimuli. (b) The same healthy person in presence of 9 Hz stimuli. (c) A patient without stimuli. (d) The same patient in presence of 9 Hz stimuli.](image)
response of migraine patients with aura. Our results are consistent with current theories about the role of subcortical structures in migraine. Since brainstem is active in migraine, it has been proposed, as a unifying concept, that brainstem regions concerned with neural mechanisms of synchrony are dysfunctional. Cor-

tex, in migraine brains, is thus misled by a dysfunctional gating system; normal light is unpleasant, normal sound uncomfortable and, probably, normal pulsing of vessels felt as pain. On the mathematical side, our results confirm the usefulness of the analytic signal technique to study physiological time series.

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