Abnormal effective connectivity in migraine with aura under photic stimulation

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Migraine patients with aura show a peculiar pattern of visual reactivity compared with those of migraine patients without aura: an increased effective connectivity, connected to a reduced synchronisation among EEG channels, for frequencies in the beta band. The effective connectivity is evaluated in terms of the Granger causality. This anomalous response to visual stimuli may play a crucial role in the progression of spreading depression and clinical evidences of aura symptoms.

Important information on the structure of complex systems can be obtained by measuring to what extent the individual components exchange information among each other. Transfer entropy [1, 2] and Granger causality [3–6] have emerged in recent years as leading statistical techniques to detect cause-effect relationships between time series; they are equivalent in the case of Gaussian stochastic variables [7]. These approaches provide further insights on the architecture of complex systems, in addition to those from correlation and synchronization analysis [8–10]. In neuroscience, interdependencies estimated by correlation or spectral coherence are referred to as functional connectivity, whilst effective connectivity is a notion related to Granger causality or transfer entropy [11]; the relationship between functional and effective connectivity in the cortex represents a significant challenge to present-day neuroscience [12–15].

Migraine, an incapacitating disorder of neurovascular origin, consists of attacks of headache, accompanied by autonomic and possibly neurological symptoms [16]. This pathology affects a relevant fraction of the general population and represents a social problem. The study of phase synchronization in EEG rhythms showed a pattern of alpha rhythm (8-12.5 Hz) hyper-synchronization under repetitive flash stimulation in migraine without aura patients, opposite to a de-synchronization trend in non-migraine subjects [17]; this nonlinear EEG pattern was found to be modulated by anti-epileptic drugs [18]. Approximately one-third of people who suffer migraine headaches perceive an aura (visual abnormality lasting 10-30 minutes) as a sign that the migraine will soon occur [19]. There are evidences [20] of relationships between migraine aura and the spreading depression (SD) phenomenon (a wave of electrophysiological hyperactivity followed by a wave of inhibition [21]) but the link between SD and headache is far to be explained in humans [22]. SD in clinically less conspicuous or extended brain regions may be the trigger of migraine attacks ostensibly without a "perceived" aura [23], so it may be plausible that, migraine with and without aura may differ for those neuronal factors favoring the clinical expression of SD phenomenon.

The question we address here is the following: how does the response of aura migraine patients, to external stimuli, differ from those of patients without aura? We show that, in presence of visual stimulations, migraineurs with aura show a pattern of increased effective connectivity between EEG channels in the beta band, and correspondingly a decrease of the synchronization between channels. This variation of connectivity, due to stimuli, is statistically significant for migraine with aura: we re-
Our data are as follows. EEG is recorded from 19 patients (7 males, 20-44 age) affected by migraine with aura, 19 (4 males, 21-45 age) patients affected by migraine without aura, and from 11 healthy subjects (control group, 3 males, 20-46 age). All patients are in the interictal state, the time from the end of the last attack being at least 72 h. No patient was under preventive treatment nor had assumed symptomatic drugs in the 72 hours preceding the recording session. During the acquisition, flash stimuli are presented at a rate of 9-18-21-24-27 Hz; also EEG in the absence of stimuli (base) is recorded. Each frequency of stimulation is delivered by a flash with 0.2 J luminance for about 20 sec. EEG data are recorded by six scalp electrodes: two occipital channels (O1 and O2), two parietal ones (P3 and P4), a central electrode (Cz) and a frontal one (Fz); the sampling rate is 256 Hz, and the EEG is digitally filtered off.

FIG. 2: (Top left) The nonlinear Granger causality of EEGs filtered in the beta band, averaged over pairs of channels and over subjects in the classes, is depicted for aura patients (stars), no aura patients (empty circles) and controls (empty squares) for basal condition and as a function of the frequency of stimulations. A Gaussian kernel with $\sigma = 10$ is used. We also make the supervised analysis (hypothesis testing) of the nonlinear Granger causality, averaged over pairs of channels, in the beta band. The probabilities that the measured values from two classes were drawn from the same distribution, evaluated by $t$ test, are depicted: aura vs controls (top right) aura vs no aura (bottom left) and aura vs controls (bottom right). Dashed lines correspond to the significance threshold at 5% after Bonferroni’s correction. The ANOVA [28], taking the nonlinear Granger causality as variable, the diagnosis (migraine with aura vs migraine without aura vs controls) and the frequency of stimulation (9-18-21-24-27 Hz) as factors, yields the $F$ values 377.35, 8.36 and 3.38 for diagnosis, frequency and interaction respectively; all the three factors are thus recognized as significant.

mark that in our knowledge neurophysiological patterns separating migraine with and without aura have been rarely detected [24], nor relevant differences in regard to visual reactivity [23].

Next, we describe our findings. Firstly we investigate the alpha band hyper-synchronization phenomenon [17] in presence of flash stimuli. The pattern of [17] is confirmed for migraineurs without aura, whilst patients with aura do not show alpha band hyper-synchronization in presence of light stimuli: in this range of frequencies, aura patients seem to behave as controls.

Moving to higher frequencies (beta band, 12.5-30 Hz), instead, we find a peculiar pattern of visual reactivity for aura patients. We set the order of the regression model equal to $m = 6$ [26] and evaluate the linear Granger causality in the beta band [27]: linear causalities are weak and show significant differences among classes only at 18 Hz stimulations, see figure (1). On the other hand, evaluating the nonlinear Granger causality among the filtered EEG signals with the kernel approach described in [6] and a Gaussian kernel, we find that aura migraine patients exhibit increased values of causality in presence of stimuli, whilst controls and no aura patients do not show significant variation w.r.t. basal conditions. In particular the discrimination between aura and no-aura patients is excellent in presence of flash stimuli. Figure (2) refers to $\sigma = 10$ as the width of the Gaussian kernel, however the results are robust to variations of $\sigma$.

A topographic analysis is also performed: for each electrode, we evaluate the total incoming causality (the sum of the causalities from the other electrodes to the electrode under consideration) as well as the total outgoing causality (the sum of the causalities from the electrode under consideration to the other electrodes). In figure (3) we depict these quantities for the three classes at 18 Hz stimulations in the beta band: it shows that the phenomenon is diffuse over the scalp.

Use of the Gaussian kernel ensures that all orders of line by a filter with a band-pass 0.3-30 Hz. Our data are as follows. EEG is recorded from 19 patients (7 males, 20-44 age) affected by migraine with aura, 19 (4 males, 21-45 age) patients affected by migraine without aura, and from 11 healthy subjects (control group, 3 males, 20-46 age). All patients are in the interictal state, the time from the end of the last attack being at least 72 h. No patient was under preventive treatment nor had assumed symptomatic drugs in the 72 hours preceding the recording session. During the acquisition, flash stimuli are presented at a rate of 9-18-21-24-27 Hz; also EEG in the absence of stimuli (base) is recorded. Each frequency of stimulation is delivered by a flash with 0.2 J luminance for about 20 sec. EEG data are recorded by six scalp electrodes: two occipital channels (O1 and O2), two parietal ones (P3 and P4), a central electrode (Cz) and a frontal one (Fz); the sampling rate is 256 Hz, and the EEG is digitally filtered off.
nonlinearities are taken into account. If one considers only nonlinearities up to the second order, weaker causalities are detected and less discriminating power is obtained, see figure [4], where we describe the application of nonlinear Granger causality with a polynomial kernel of degree two. We conclude that a relevant amount of nonlinear information transmission characterizes this phenomenon.

Turning to synchronization, we consider the Pearson linear correlation between channels and find that the increased flow of information, due to flash stimuli, is connected to weakening of the correlations between them. In figure [5] we depict the linear correlation between signals filtered in the beta band, averaged over all pairs of channels; in presence of light stimulations the strength of correlations decreases for aura patients. We find similar results also in terms of the coherence function averaged in the beta band, see figure [6], as well as for the beta band phase synchronization [29].

We also quantify the separation among classes in terms of the ROC area [30], which is directly related to the separation of two conditional distributions, and measures the discrimination ability of the forecast. For any frequency of stimulation, using the Gaussian kernel Granger causality we obtain a roc area equal to 0.87 for aura vs no-aura patients. A similar result is found using the linear correlation, roc area equal to 0.82 for aura vs no-aura at all frequencies.

Summarizing, we have described for the first time a neurophysiological pattern which seems peculiar of migraine patients perceiving visual aura, where the loss of synchronization between channels, due to light, induces stronger statistical causal connections among them, diffuse over the scalp. This pattern is characterized by nonlinear transfer of information among channels and provides excellent discrimination between aura and no-aura patients. The biological implications of this complex phenomenon in facilitating SD progression and aura symptoms perception is the challenge for a better understanding of migraine pathophysiology.
FIG. 6: (Top left) The coherence function of EEGs in the beta band, averaged over pairs of channels and over subjects in the classes, is depicted for aura patients (stars), no aura patients (empty circles) and controls (empty squares) for basal condition and as a function of the frequency of stimulations. We also make the supervised analysis (hypothesis testing) of the coherence, averaged over pairs of channels, in the beta band. The probabilities that the measured values from two classes were drawn from the same distribution, evaluated by $t$ test, are depicted: aura vs controls (top right) aura vs no aura (bottom left) and aura vs controls (bottom right). Dashed lines correspond to the significance threshold at 5% after Bonferroni’s correction.

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