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The measure of randomness by leave-one-out prediction error in the analysis of EEG after laser painful stimulation in healthy subjects and migraine patients

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Abstract

Objective: We aimed to perform a quantitative analysis of event-related modulation of EEG activity, resulting from a not-warned and a warned paradigm of painful laser stimulation, in migraine patients and controls, by the use of a novel analysis, based upon a parametric approach to measure predictability of short and noisy time series.

Methods: Ten migraine patients were evaluated during the not-symptomatic phase and compared to seven age and sex matched controls. The dorsum of the right hand and the right supraorbital zone were stimulated by a painful CO_2 laser, in presence or in absence of a visual warning stimulus. An analysis time of 1 s after the stimulus was submitted to a time–frequency analysis by a complex Morlet wavelet and to a cross-correlation analysis, in order to detect the development of EEG changes and the most activated cortical regions. A parametric approach to measure predictability of short and noisy time series was applied, where time series were modeled by leave-one-out (LOO) error.

Results: The averaged laser-evoked potentials features were similar between the two groups in the alerted and not alerted condition. A strong reset of the beta rhythms after the painful stimuli was seen for three groups of electrodes along the midline in patients and controls: the predictability of the series induced by the laser stimulus changed very differently in controls and patients. The separation was more evident after the warning signal, leading to a separation with *P*-values of 0.0046 for both the hand and the face.

Discussion: As painful stimulus causes organization of the local activity in cortex, EEG series become more predictable after stimulation. This phenomenon was less evident in migraine, as a sign of an inadequate cortical reactivity to pain.

Significance: The LOO method enabled to show in migraine subtle changes in the cortical response to pain.

Keywords: EEG analysis; Migraine; Laser stimulation

1. Introduction

Painful stimuli delivered by infrared laser stimulators elicit laser-evoked potentials (LEP) or magnetic fields in respective electroencephalogram (EEG) and magnetoencephalogram (MEG). Evidence is reviewed that LEP represent a series of event-related potentials (ERP) that depend on vigilance and arousal, selective spatial attention and contextual task variables. (Lorenz and Garcia-Larrea, 2003). Attention and distraction in turn reduce or enhance the activation of cortical areas devoted to pain elaboration, which is expressed by LEPs amplitude. Event-related modulation of EEG spectral energy is another measure of cortical activation, which has been demonstrated during multiple behaviors

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including movement (Crone et al., 1998; Ohara et al., 2000a), vision (Tallon-Baudry et al., 1996), audition (Crone et al., 2001a), and language (Crone et al., 2001b). In a previous study, wavelet time–frequency analysis and bandpass filtering was employed to test Event-related desinchronization (ERD) quantitatively in subdural electrocorticographic recordings while subjects either attended to, or were distracted from, a painful cutaneous laser stimulus. (Ohara et al., 2004). In all subjects, ERD was more widespread and intense during attention to laser stimuli than during distraction from the stimuli.

Several LEPs studies have showed an abnormal pattern of cortical activation under painful stimuli in migraine patients, consisting of reduced habituation to repetitive stimuli (de Tommaso et al., 2005; Valeriani et al., 2003) and reduced inhibitory effect of distraction (de Tommaso et al., 2003): LEPs amplitude was employed as measure of variation between different states of attention, even if the occurrence of artefacts may reduce the clearness of the peaks, limiting the detection of subtle modifications.

The EEG time–frequency wavelet analysis, is a valid method to show the development of EEG frequencies modifications after painful stimuli, according to Ohara et al. (2004). In addition, other methods may be employed in order to detect the modifications induced by laser stimuli on EEG activity in migraine patients: in this study, we performed a novel analysis, based upon a cross-trial correlation task, in order to select the most activated cortical regions, followed by a parametric approach to measure predictability of short and noisy time series, used to quantify predictability (Vapnik and Vapnik, 1998). This approach has already been used in Ancona et al. (2005) to analyse systolic arterial pressure time series from healthy subjects and chronic heart failure patients.

The basic idea in this approach is that different physiological states may be characterized in terms of predictability of time series. The predictability is connected to the complexity of the series itself, resulting from complicated regulation mechanisms: here, we extend and elaborate previous findings showing its applicability in the analysis of EEG activity evoked by CO_2 laser painful stimulation.

In the present study, we aimed to perform a quantitative analysis of event-related modulation of EEG activity, resulting from a not-warned and a warned paradigm of painful laser stimulation, in order to detect subtle modifications of cortical activity in migraine patients. We choose to test only the properties of sustained attention to laser stimuli, without performing any contemporary distraction task, which may cause activation of several cortical areas during EEG recording.

2. Materials and methods

2.1. Subjects

Ten patients suffering from migraine without aura (Headache Classification Committee, 2004) were submitted to CO_2 laser stimulation, during the not-symptomatic phase. They were seven females and three males, aged 23–40. (mean age 30.1 + 6.9) All patients were diagnosed after six months' follow-up. Patients with general medical, neurological, or psychiatric diseases, and patients who were taking psycho-active drugs, or prophylactic treatment for headache, or who were assessed as overusing analgesic drugs in the last 2 months, were excluded from the study. All patients were evaluated at least 72 h after the end of the critical migraine phase (mean 75 + 2.1 h) and well before the next attack (mean 48 + 8.2 h), verified by the headache diary during a following clinical examination. Seven sex and age matched healthy subjects were also submitted to the experimental procedure (five females and two males, aged 22–41—mean 30.3 + 5.5).

The experiment was undertaken with the understanding and written consent of each subject and with the ethical approval of the Neurological and Psychiatric Department of Bari University.

2.2. Laser stimulation paradigm

CO_2 laser stimulation was delivered on the skin of the dorsum of the right hand and the right supraorbital zone. The pain stimulus was laser pulses (wavelength 10.6 μm) generated by a CO_2 laser (Neurolas, Electronic Engineering, Florence, Italy; www.elengroup.com). The beam diameter was 2.5 mm, and the duration of the stimulus pulse was 25 ms. We used a fixed intensity set at 7.5 W for both the hand and the supraorbital zone (Bihel et al., 1984). For each site of stimulation, 40 laser stimuli were delivered. A series of 20 stimuli was delivered without any warning signal and a random ISI, ranging from 10 to 20 s: in another series, all stimuli were preceded by a warning flash, followed by a fix interval of 3 s, after which the painful stimulation occurred. In each series of stimulation, subjects were requested to count the stimuli. The sequence of warned and not-warned tasks in the two sites of stimulation was randomly assigned in all cases. Subjects were requested to rate the intensity of painful stimuli at the end of the warned and the unattended trials, using a 0–100 VAS.

2.3. Data acquisition

Signals were recorded through 19 disk electrodes, according to the 10–20 international system (impedance below 5000 Ω), referring to the nasion with the ground at Fpz. Signals were amplified and stored on a biopotential analyzer at a sampling rate of 256 Hz. (MICROMED

System Plus; MICROMED, Mogliano Veneto, Italy; www.micromed-it.com).

3. Data analysis

3.1. LEPs analysis

The latency and amplitude of the negative–positive deflection (N–P complex) was measured at the vertex, after a post-averaging of each series and an application of a filter bandpass 0,5–100 Hz in a 1 s time analysis.

3.2. Time–frequency analysis

We used a complex Morlet wavelet to obtain a time–frequency representation of the EEG signal in order to estimate each individual subject's reactive EEG frequency bands. The normalized complex Morlet wavelet is defined as $w(t,f_0) = (\sigma 2\pi) - 1/4\exp(-t2/2\sigma 2)\exp(2\pi i f_0 t)$, where i is the imaginary unit, f_0 is the center frequency, and σ is the width of the wavelet. A constant ratio at $2\pi f_0\sigma = 7$ was used, according to previous studies, and center frequencies ranging from 1 to 40 Hz in steps of 0.5 Hz. The modulus of the transform expresses oscillation amplitude as a function of time and frequency. We refer the reader to Ohara et al. (2004) for details of the procedure.

3.3. Cross-trial correlation analysis

All EEG signals have been filtered in the delta (1–4), theta (4,5–7,5 Hz), alpha (8–12 Hz) and beta bands (12.5–30 Hz).

In order to test to what extent the brain rhythms are reset after the stimulus, we investigate the cross-correlation of filtered time series from pairs of electrodes. In the case of k stimuli, for the electrodes x and y, the cross-trial cross-correlation is defined as:

$$C_{xy}(t) = \frac{\sum_{j=1}^{k} x(t+\tau_j)y(t+\tau_j)}{\sqrt{\left[\sum_{j=1}^{k} x^2(t+\tau_j)\right]}\sqrt{\left[\sum_{j=1}^{k} y^2(t+\tau_j)\right]}}$$

where τ_j is the instant in which the jth stimulus is delivered. The quantity C is normalized ($-1 \le C \le 1$), and it assumes large values in presence of a strong reset triggered by the stimuli.

3.4. Leave-one-out error

As a measure of predictability, we considered the leave-one-out (LOO) prediction error indicator, introduced and discussed in detail in Ancona et al. (2005). Here, we briefly recall the main properties of this approach. Let us denote $\{xi\}$, $i=1,\ldots,N$, a physiological time series, which we assume to be stationary (this assumption is justified in the case of short length of the recording). In the preprocessing stage, the time series is normalized to have zero mean and unit variance. We fix the length of a window m, and for $k=1$–M (where $M=N-m$), we denote $Xk=(xk+m-1,\ldots, xk)$ and $Yk=xk+m$; we treat these quantities as M realizations of the stochastic variables X (input variables) and Y (output variable) with unknown probability distribution $P(X,Y)$.

The estimator f: $X \to Y$. in our approach has the form:

$$Y = f(X) = \sum_{i=1}^{M} c_i K(X_i, X)$$

where the kernel $K(X,X')$ is a positive definite symmetric function, and coefficients c_i are given by

$$c_i = \sum_{j=1}^{M} (K + \lambda I)_{ij}^{-1} Y_j$$

K being an $M \times M$ matrix with generic element $K_{ij} = K(X_i,X_j)$, and λ is the regularization parameter. This predictor corresponds to a linear predictor in the feature space spanned by the eigenvectors of the integral operator determined by K. Many choices of the kernel function are possible, for example, the polynomial kernel of degree p has the form $K(X,X\text{prime};) = (1+XX')P$ (the corresponding features are made of all the powers of X up to the Pth). The RBF Gaussian kernel is $K(X,X) = \exp\{-(||X-X||2/2\sigma 2)\}$and deals with all the degrees of nonlinearity of X: the width σ plays a role similar to that played by the regularization parameter, i.e. it must be tuned to avoid overfitting. As a measure of the generalization ability of the trained model, we consider the leave-one-out error ε, i.e. the average empirical square error when the data point, whose error is under consideration, is removed from the training set. It can be calculated as follows:

$$\varepsilon = \frac{1}{M}\sum_{i=1}^{M}\left(\frac{Y_i - \sum_{j=1}^{M} K_{ij}c_j}{1 - G_{ii}}\right)^2$$

where the matrix G is equal to $K(K+\lambda I)-1$. We conclude remarking the interesting properties of the class of models we are dealing with. The most important is that such models have high generalization capacity. This means that they are able to predict complex signals when a finite and small number of observations of the signal itself are available. Moreover, the degree of nonlinearity present in the modeling, introduced by this method, may be easily controlled. They allow an easy calculation of the leave-one-out error ε, the quantity that we use to quantify predictability. Finally, this approach generalizes the classical autoregressive (AR) approach to time series analysis, which is recovered for $P=1$ polynomial kernel in the limit $\lambda=0$.

Turning back to our problem, filtered EEG series were modeled using a Gaussian kernel with $m=32$, $\sigma=6$ and regularization parameter $\lambda=0.01$.

For each patient and for each electrode, we extracted a time series after each stimulus, starting from $\tau_j+\tau_r$, where τ_j is the instant when the stimulus is delivered and r_j is a reaction time, equal to 0.25 and 0.35 s for stimulus delivered on face and hand, respectively. The same was done after the flash used as warning. The duration of the series is 1 s ($N=256$ points), corresponding to the average post-stimulus correlation period.

Furthermore, for every post-stimulus series, a time series of equal length was extracted by the EEG before the stimulus, in order to have a control sample.

For each series we calculated the LOO error, then, averaging on the whole number of stimuli, we got one value of the error for every channel and every subject, in the four acquisition protocols.

3.5. Power spectral density

As an indicator of the spectral power in beta band we evaluated the power spectral density using the Welch method. We employed half-overlapping Hanning windows with a length of 0.25 s. Then, the PSD was obtained integrating between 12.5 and 30 Hz and averaging.

The series were extracted taking 256 points (1 s) before and the stimulus and 256 points after the reaction time to the stimulus the same way as described above.

4. Results

4.1. LEPs analysis

The latencies and amplitudes of the N–P peak measured at the vertex, were not significantly different in basal conditions between patients and controls, as showed by one-way ANOVA test with cases as factor (hand latencies: $P=$ 0.89 hand amplitude $P=0.32$; face latencies: $P=0.89$; face amplitude $P=076$). (Fig. 1) When the ANOVA was employed with cases, site of stimulation and condition (not-warned and warned stimulation pattern) as factors, the results were also not significant (for latencies: cases$\times$ condition $P=0.43$; cases$\times$condition$\times$site $P=0.79$: for amplitude: cases$\times$condition: $P=0.23$, cases$\times$condition$\times$ site $P=0.45$). Similarly, the pain rating showed a slight increase when the stimuli were delivered after the warning signal, though it was not significant in patients and controls between the two conditions (Fig. 1).

4.2. Time–frequency analysis

The time–frequency analysis over all the electrodes, revealed that on CZ derivation the ongoing EEG showed the most evident modifications: painful thermal stimulation induced transient power increase of alpha and beta bands during the not-warned stimulation of the hand and the face in both patients and controls: it was followed in control subjects by a reduction of alpha and beta power, which were more evident after the warning signal. In migraine patients, the beta band showed to be less enhanced by the painful stimulus in the first 500 ms, and its increase was more evident in the alerting condition. In healthy subjects, the averaged LEPs corresponded to the alpha-beta power increase, specially in respect with the later positive component. In migraine patients, the alpha rhythm increase appeared to be more persisting in time, after the resolution of the averaged LEPs (Fig. 1).

4.3. Cross-trial correlation analysis

The evaluation of this parameter revealed a strong reset of the beta rhythms after the painful stimuli for three groups of electrodes. Electrodes FZ, F3 and F4 (F) are found to be strongly intercorrelated. The same happened for the groups C3, CZ, C4 (C) and P3, PZ, P4 (P). The correlation persisted for a long interval of time ($\sim$1 s).

In Fig. 2 is plotted C versus time for the couple FZ–F3 and for the couple O1–O2, for a typical patient. The dotted line on 0 represents the time of delivery of the stimulus. After the reaction time, the value of C goes close to one for the pair FZ–F3, and then goes back to pre-stimulus values after more than 1 s. This does not happen for the pair O1–O2, that is close to each other, and thus reasonably intercorrelated, but this correlation does not increase after the stimulus.

For the same patient, in Fig. 2 we report a map of the correlations between all the couples of electrodes. The presence of three inter-correlated groups corresponds to three 3×3 almost white squares along the diagonal. The same qualitative patterns are found in all the remaining patients and in all the controls, for all the acquisition protocols.

From these results we can state, that signals from electrodes F, C and P represent the brain areas most sensitive to painful stimuli, and therefore in the subsequent analysis we will concentrate on these nine electrodes.

4.4. LOO error and power spectral density

In control subjects, after the painful stimulus without flash, there was a significant increase in predictability of the series, and the values of the error separated the two states with a P-value of 0.0012 for the hand and 0.0023 for the face.

When the stimulus was delivered after the flash, the predictability increased even further, and in this case, we found P-values of 0.0006 for both hand and face.

For migraine patients we observed the same trend even if after the laser stimulus migraine patients displayed a

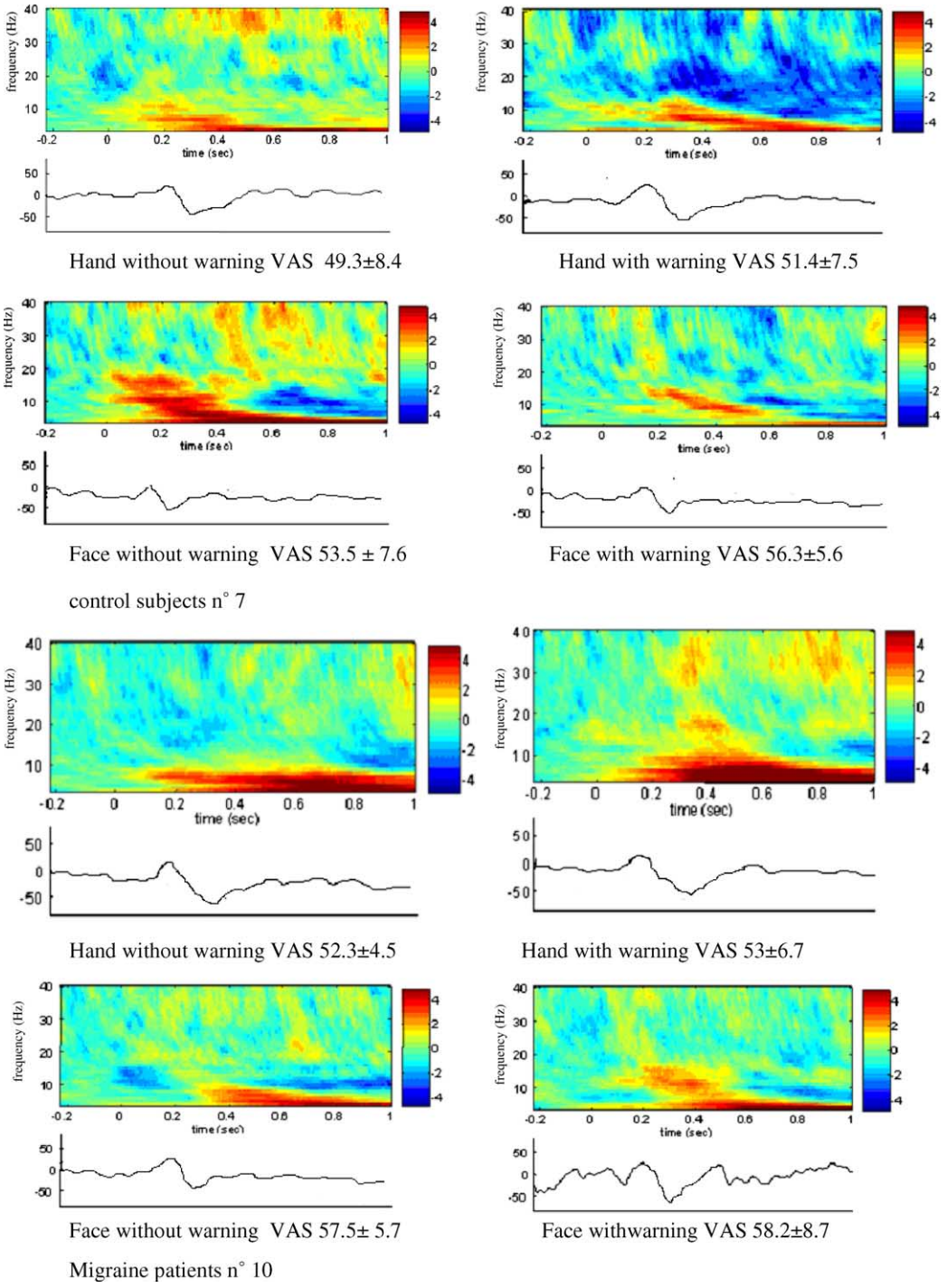

Fig. 1. Time–frequency representation of EEG spectral response to painful stimulation on the vertex derivation. The average values across all patients and controls were computed. The averaged LEPs were also represented. Wavelet transform was used to compute the time–frequency representation of EEG spectral response. Painful thermal stimulation induced transient power increase (ERS, warm colors) in the alpha and beta range. After the warning stimulus, a power decrease (ERD, cool colors) in the beta range occurred in controls.

significant increase in predictability only when the painful stimulus was delivered after the flash, with *P*-values of 0.0070 for the hand and 0.0379 for the supraorbital zone.

The mean values of the LOO error in basal conditions, after the flash, and after the painful stimulus are reported in Table 1.

The values of PSD displayed a slight decrease after the warned and unwarned stimulus, for every subject, but this change was in no case statistically meaningful.

During the states of basal acquisition it was not possible to discriminate between control subjects and patients using the predictability of the series or the power spectral density.

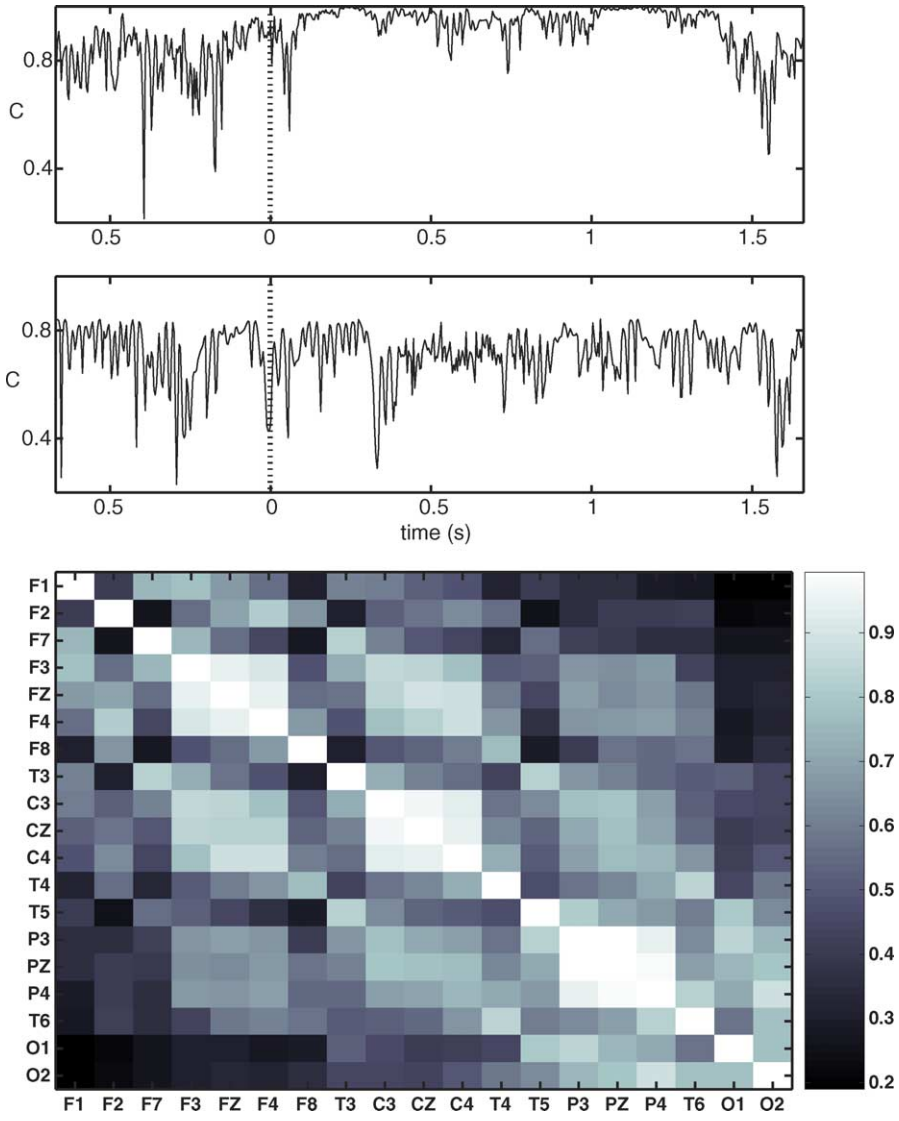

Fig. 2. Top: Cross-trial cross-correlation *C* is plotted versus time for the pair FZ–F3 (up) and for the pair O1–O2 (down), for a typical patient; Bottom: The map (with grey level scale) representing the cross-trial cross-correlation (averaged over the interval of 1 s after the stimulus) between all pairs of electrodes, for the same patient.

After the painful stimulus the predictability of the series changed very differently in controls and patients, leading to a separation with *P*-values of 0.0046 for the hand and 0.0068 for the face. When the stimulus was preceded by the flash the *P*-values were 0.0046 for both hand and face.

The power spectral density separated the two classes with *P*-values of 0.0330 for the hand and 0.0185 for the face when the pain was dispensed without warning. In case of previous warning the *P*-values turned to be 0.0250 for the hand and 0.0136 for the supraorbital zone.

5. Discussion

Here, we have reported an evaluation of laser-induced EEG changes, using a novel statistic approach, which was able to show subtle brain electrical activity modification in migraine patients after painful stimulation, not outlined by LEPs features changes. In fact, the latencies and amplitude of LEPs were unmodified under the different conditions of warned and not-warned stimulation. In a recent review, Lorenz and Garcia Larrea (2003) stated that distraction during an alternative cognitive task exerts a clear inhibition on LEPs amplitude, for an inter-model attentional effect: in similar experimental conditions, migraine patients showed different LEPs features in comparison with not-migraine subjects (de Tommaso et al., 2003). In the present study, the condition of sustained attention toward the painful stimuli was only enhanced by a warning signals, with a slight increase of pain rating, which was not linked with LEPs amplitude increase, either in patients nor in controls. The time–frequency analysis reproduced the findings described

Table 1
The values referred to 10 migraine patients and seven controls (in the parentheses)

	Hand, no flash	Hand, with flash	Face, no flash	Face, with flash
Mean values of the LOO error				
Basal	0.0399 (0.0344)		0.0390 (0.0349)	
After stimulus	0.0326 (0.0257)	0.0309 (0.0244)	0.0323 (0.0242)	0.0313 (0.0261)
Mean values of the power spectral density (PSD)				
Basal	162.16 (120.34)		157.65 (111.59)	
After stimulus	150.20 (85.06)	146.41 (87.92)	161.43 (86.28)	146.11 (83.37)
Discrimination *P*-values between controls and patients with LOO errors				
Basal	0.0553		0.2698	
After stimulus	0.0046	0.0046	0.0068	0.0046
Discrimination *P*-values between controls and patients with PSD				
Basal	0.6391		0.4163	
After stimulus	0.0330	0.0250	0.0185	0.0136

by Mouraux and Plaghki (2004) and Ohara et al. (2004) in basal conditions, consisting of alpha and beta power increase after laser stimulus, evident in both migraine patients and control subjects. Our experimental trial of increasing sustained attention by alerting signal provoked a reduction of EEG power mainly in the beta band in control subjects. The time–frequency analysis was confirmed to be a valid method to follow the EEG changes after laser stimulus, showing modifications in alpha and beta power, which were only partly time-correlated to the averaged LEPs, suggesting a long-persisting cortical activation.

The cross-correlation method showed that in both patients and controls the maximal activation after painful laser stimulus regarded the beta rhythm over the midline derivations, which may reflect the mesial cortical regions and particularly the cingulate cortex, which generates the later cortical LEPs (Garcia Larrea et al., 2003).

The further analysis revealed consistent changes of cortical activation pattern between patients and controls. Using the formalism of machine learning, we have presented an approach to time series modeling which generalizes the autoregressive approach in two ways: (i) the model was regularized; (ii) nonlinearity was introduced. This allows measuring randomness in physiological time series by means of the leave-one-out error. We have shown application of the method to simulated time series and to the analysis of electroencephalographic signals from healthy subjects and migraineurs, after painful stimulation. The analysis of simulated data has revealed that the presence of structure in data is connected with the presence of a minimum of the LOO error as the regularizing parameter is varied.

Concerning the physiological application, use of the leave-one-out error allowed to discover that migraine patients show an inadequate response, in terms of reset-induced increase of predictability, to painful stimulation.

As painful stimulus causes organization of the local activity in cortex, EEG series become more predictable after stimulation. The increase of EEG predictability after painful stimulation may be a sign of cortical reactivity to external conditions: the cortex may reduce the degree of randomness in order to adequately receive and elaborate the novel painful stimulus. Of course, in the condition of warned stimulation, the cortex appears more prone to receive the pain signal, as shown by an increase in predictability after the visual warning, evident in not-migraine subjects. In migraine patients, the tendency toward a less pronounced increase in predictability after the laser stimulus, may be explained by an inadequate cortical response to pain, which becomes more efficacious only after the warning stimulus, which provoked a significant predictability change in respect with basal condition. These modifications of EEG predictability, corresponded in controls to a general decrease of beta band spectral density over the whole analysed time after the painful laser stimulus, specially in the alerted condition: also this phenomenon was less evident in migraine subjects. These methods enabled to show in migraine patients an altered cortical response to pain in conditions of sustained attention, which were not outlined by the LEP features. This phenomenon was present on both the face and the hand, so it was generalized and not confined to the trigeminal zone: it may be linked with an abnormal level of cortical excitability, which was suggested by the results of the neuro-physiological studies in migraine (Ambrosini et al., 2003), though further evidences are needed to interpret the modifications of EEG predictability as a result of cortical hypo or hyper-excitability. The psycho-physiological significance of this cortical behavior is also difficult to interpret. In our previous study (de Tommaso et al., 2003), the cortical elaboration of pain was not inhibited during a contemporary arithmetic task. In a recent fMRI study, distraction was associated with a significant reduction of pain-related activation in multiple brain areas, particularly in the so-called ‘medial pain system’, and to an increased activation of the cingulo-frontal cortex,the periaquaeductal gray (PAG) and the posterior thalamus: according to these results, the cingulo-frontal cortex may exert top–down influences on the PAG and posterior thalamus to gate pain modulation during distraction. (Valeta et al., 2004). Our method was very sensitive to the stimulus-related EEG changes, though not indicative of their source: the location of the maximal cross-correlation around the midline, without any side prevalence, may reflect the activation of multiple brain areas, firstly the cingulo-frontal cortex, which generates the later LEPs (Garcia Larrea et al., 2003). If the painful stimuli should not cause in migraine an adequate recruitment of these cortical regions, the pain modulation

system may be compromised and not well activated during different conditions: this phenomenon may concur to the onset and the persisting of headache.

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