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Probing cortical excitability using cross-frequency coupling in intracranial EEG recordings: a new method for seizure prediction

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Abstract—**The need of a reliable seizure prediction is motivated by the 50 million people in the world suffering from epilepsy, of whom 30% have no control on seizures with current pharmacological treatments. Seizure prediction research holds great promise for such patients, since an effective algorithm will enable the development of a closed-loop system that intervenes before the clinical onset of a seizure. As a step toward practical implementation of this technology, we present a new method based on a measure of brain excitability identified by couplings between low-frequency phases and high-frequency amplitudes of brain oscillations. The proposed method was applied to long-term intracranial recordings of 20 patients with partial epilepsy, for a total of 267 seizures and more than 3400-hour-long interictal activities. We found that our predictor was in 50% of cases better than chance, with an average sensitivity of 98.9% and false prediction rate of 1.84/hour. From these observations, we concluded that our method enables a new quantitative way to identify preictal states with a high risk of seizure generation**

I. Introduction

EPILEPTIC seizures are not randomly occurring events, but they are instead a product of slow changes in brain excitability evolving over long timescales and predisposing the brain to epileptic activity. Indeed, over recent years, there are growing evidences suggesting that the transition from the interictal state (far from seizures) to the ictal state (seizure) may be preceded, from minutes to hours, by pre-ictal clinical, metabolic, or electrical changes [1]. In this context, slow cortical potentials are assumed to provide a threshold controlling the excitability of cortical networks that could influence seizure susceptibility [2]. In particular, the slow oscillations have the ability to trigger and group local high-frequency oscillations and these cross-frequency couplings may be a signature of global cortical excitability [3]. We investigated the fluctuations of couplings between the low-frequency phase (<10 Hz) and high-frequency amplitudes (>40Hz) in continuous and long-term intracranial electroencephalographic recordings (EEG) of epileptic patients. Special attention was focused on their preictal fluctuations before electroclinical seizures. In order to study whether these changes could specifically identify an increased risk of epileptic seizures, we analyzed continuous and long-term recordings covering 1-2 weeks of EEG monitoring in order to comprise the full spectrum of physiological and pathophysiological states for an individual patient [1]. An alarm warning was triggered if the number of intracranial contacts with a determined coupling phase crosses a critical threshold. Both sensitivity and false prediction rate were assessed relative to the duration of the expected preictal time (10, 30, 60min) and were statistically validated by an analytical random predictor to test whether they perform above chance level. To the best of our knowledge, this is the first attempt that uses cross-frequency phase-amplitude coupling in the field of seizure prediction.

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II. Methods

A. Cross-Frequency Coupling

Recent studies indicate that brain oscillations do not exist in isolation, but they rather interact across different temporal and spectral scales giving rise to a variety of cross-frequency coupling dynamics [4]. As already reported in human intracranial recordings [5], we examined the coupling between the phase of low frequency rhythms (delta: 0.5-3Hz and theta: 3-8Hz) and the amplitude of high frequency oscillations (low gamma, LG: 40-70Hz and high gamma, HG: 70-140Hz). Although, several methods has been proposed to assess cross-frequency coupling, none has been chosen as the gold standard. In this study, we implemented a similar methodology to the one proposed by [6]:

1) Filtering stage: raw EEG signals were filtered in the four mentioned frequency bands. In order to prevent phase distortion, we applied forward-backward IIR filters, whose coefficients were computed with an 8-order Butterworth function. Specifically, for a narrow-band signal $x(t)$, the Hilbert transform can be used to obtain its analytical representation $x_a(t)$ whose angle φ_x corresponds to the instantaneous phase and magnitude A_x represents the envelope.

$$x_a(t) = x(t) + j\tilde{x}(t) = A_x e^{-j(\omega t+\varphi_x)} \quad (1)$$

where $\tilde{x}(t)$ is a version of $x(t)$ shifted by $\pi/2$ to eliminate its negative frequencies. We computed the phase

of delta φ_δ and theta φ_θ, as well as the amplitude envelope for low A_{LG} and high A_{HG} gamma.

2) Coupling distribution: for each pair $(\varphi_{low}, A_{high})$, we estimated the distribution of gamma (A_{LG}, A_{HG}) over the phase of slow activity $(\varphi_\delta, \varphi_\theta)$. First, the phase interval $[-\pi, \pi]$ was divided in 40 discrete bins φ_i. For the bin i, we determined the time indexes k_i of the phase vector φ_{low}, such that $\varphi_i \leq \varphi_{low}(k_i) < \varphi_{i+1}$. Since phase and envelope vectors are equally indexed, we calculated the average of the envelope vector A_{high} over k_i. If the distribution $P(i) = < A_{high} >_{\varphi_{low}} (i)$ is unimodal, it is inferred that gamma activity tends to be coupled to the phase where the maximal peak appears. In contrast, a flatter distribution suggests that both frequency bands are scarcely coupled.

3) Mean phase estimation: in order to determine the phase of coupling preferred by high frequency activity, we fitted the distribution over the binned phase φ to a probability density function. For the fitting, the von Mises distribution (circular Gaussian) was used:

$$p(\varphi) = \frac{1}{2\pi I_0(\kappa)} e^{\kappa \cos(\varphi - \mu)} \quad (2)$$

where $-\pi \leq \varphi < \pi$ and I_0 is the modified Bessel function of order . Parameters μ and $\kappa \geq 0$ are analogous to mean and variance of a normal distribution. Thus, for a particular distribution, the estimated mean value μ corresponds to the phase of coupling (φ_{coupl}). As an example, Fig. 1 shows the procedure used to estimate φ_{coupl} for an artificial sinusoidal signal $x_{sin}(t)$ [6]:

$$x_{sin}(t) = A'_{high}(t)\sin(\omega_{high}t) + A_{low}(t)\sin(\omega_{low}t) + W(t) \quad (3)$$

where $W(t)$ corresponds to Gaussian noise and A'_{high} is the amplitude of the high frequency component $A_{high}(t)$ modulated by the low frequency band:

$$A'_{high}(t) = A_{high}\frac{(1-\chi)\sin(\omega_{low}t + \varphi_{coupl}) + 1 + \chi}{2} \quad (4)$$

The variable χ is the portion of the high frequency envelope that is not modulated, varying inversely to the strength of coupling. Fig. 1 shows that the mean phases were correctly extracted for two levels of coupling χ.

B. A strategy for preictal state identification

We examined a group of 20 epileptic patients suffering from pharmaco-resistant partial epilepsy from the EPILEPSIAE database [7]. During the presurgical evaluation, intracranial EEG was recorded from depth or subdural stereotactic electrodes, to better localize epileptogenic regions for possible resection. EEG signals were continuously recorded at a sampling rate of 1024Hz, for several days (~7 days). During this period patients presented several seizures, originated at different brain regions (foci) (Table I). As a joint European project, a standardized EEG annotation protocol was developed to ensure the comparability and reliability of the seizure onset time [7]. Only seizures with clinical and electroencephalographic signs were taken into account for this analysis. If seizures were separated less than 1.5 hours, only the first seizure was considered for prediction purposes.

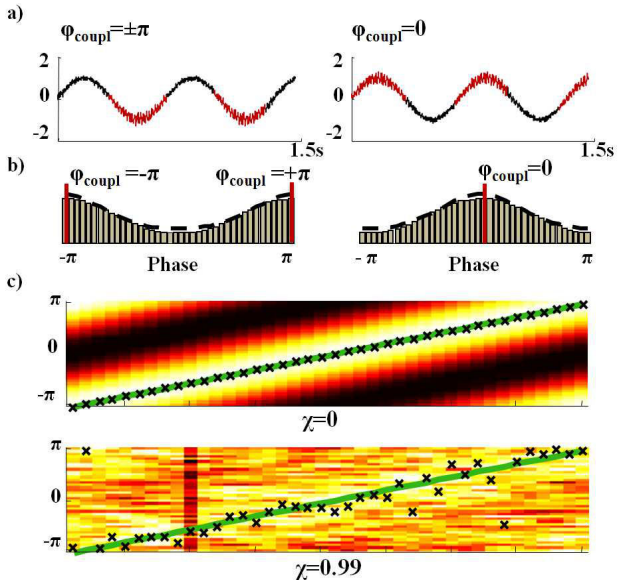

Fig. 1. Estimation of the phase of coupling on artificial data. a) Sinusoidal signal with phase-amplitude coupling: high frequency oscillations appear in red at $\pm\pi rad$ and $0rad$ of the low frequency phase. **b)** The corresponding coupling distribution and the estimated mean phase (red) **c)** Theoretical phase φ_{coupl} (green) compared with the estimated phase (cross) for strong (χ=0) and weak (χ=0.99) levels of coupling. In color the coupling distribution for several values of mean phase.

TABLE I

INFORMATION AND RESULTS FOR 20 PATIENTS. LAST COLUMN INDICATES SIGNIFICANT PATIENTS OVER σ_{low} (*) AND OVER σ_{up} (**). AVERAGE FOR THE ENTIRE AND SIGNIFICANT CASES ARE SHOWN IN THE LAST TWO ROWS. FOCI CORRESPOND TO REGIONS FRONTAL,TEMPORAL,CENTRAL,OCCIPITAL.

ID	Time (h)	Electrode	Seizures	Foci	Preictal (min)	Coupl	φ_{coupl} (rad)	Thr (%)	SS (%)	FPR (FP/h)	Significance
1	246	98	10	F	10	HG-θ	2.9	23	96.8	13.39	
2	217	96	8	T	30	LG-δ	1.3	16	96.8	6.14	
3	119	57	13	T	30	LG-θ	1.8	7	100	3.01	*
4	182	117	9	T	10	HG-δ	-0.8	22	80.6	12.84	
5	251	38	5	T	30	HG-δ	2.4	5	100	16.02	
6	163	74	9	T	10	LG-δ	1.8	8	100	15.55	
7	249	46	9	T	60	LG-θ	1.3	5	100	3.39	
8	128	115	12	T,F	10	LG-θ	1.8	14	100	0.14	**
9	155	62	14	T	10	HG-θ	0.8	5	100	1.61	**
10	150	124	7	T,F	30	LG-δ	-2.9	23	100	2.86	
11	141	48	12	F	30	HG-θ	2.4	15	100	6.97	
12	199	40	17	T	60	HG-δ	1.8	6	100	18.97	
13	124	93	15	F	10	LG-δ	0.3	42	100	0.18	**
14	229	89	16	F	10	LG-θ	0.8	24	100	3.51	**
15	113	114	10	O,T	10	HG-δ	2.4	9	100	2.07	**
16	171	69	15	T	10	LG-θ	0.8	10	90,9	2.38	**
17	119	83	22	T	10	LG-δ	-0.3	11	100	1.64	**
18	224	46	12	T	10	HG-δ	-2.9	5	100	3.04	**
19	111	83	16	F,C	10	HG-θ	2.9	41	100	3.39	**
20	142	84	36	T	10	LG-δ	0.3	8	98,3	0.48	**
Total	**3432**		**267**		**20**				**98.2**	**5.88**	**50%**
Signif.					**10**				**98.9**	**1.84**	

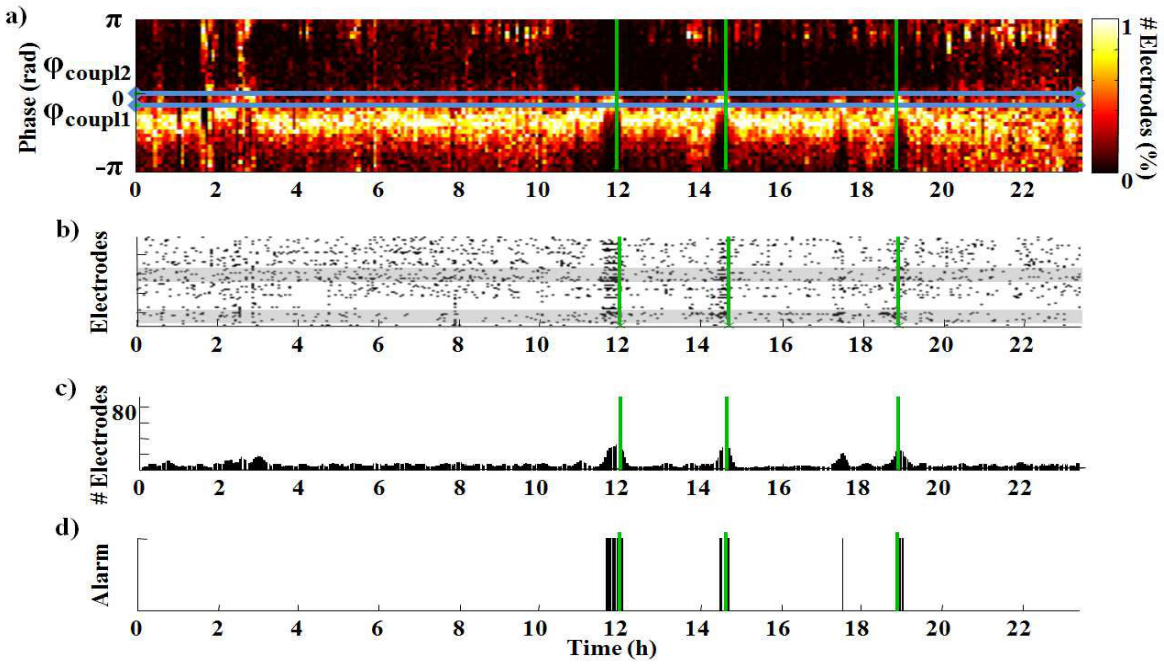

Fig. 2. Prediction based on cross-frequency coupling analysis. a) Color in the map represents the number of electrodes with different φ_{coupl} along the time. Vertical lines indicate EEG seizure onset. **b)** Intervals of phase were chosen $[\varphi_{coupl1}, \varphi_{coupl2}]$ (blue lines in **a)**). If an electrode fall in this interval, it is represented by a black point. Shadow regions indicate seizure foci electrodes **c).** The number of electrodes is summed and a threshold is applied to determine whether or not the segment is a possible preictal period. **d)** Segments in which the number of electrodes exceeds the threshold trigger an alarm.

In order to assess the ability of cross-frequency coupling to detect preictal changes, we proposed the following strategy: first, φ_{coupl} of each intracranial contact was extracted for consecutive non-overlapped windows of 1-minute. Second, the number of contacts within each phase bin was determined (Fig.2a). Third, the proportion of contacts at a specific mean phase interval $[\varphi_{coupl1}, \varphi_{coupl2}]$ was estimated over time (Fig.2 b-c). Finally, an alarm was raised when this proportion exceeded a critical threshold (Fig.2d). Both, the mean phase interval and the critical threshold, were the parameters to optimize during the performance evaluation of the proposed method. For this evaluation, we used two interdependent measures of prediction quality, the sensitivity (SS, the fraction of correctly predicted seizures) and the false prediction rate (FPR). True and false predictions were defined relative to the seizure onset time (annotated by clinicians) for different preictal durations of 10, 30 and 60 minutes. Receiving-Operating Characteristic (ROC) curves, a conventional way to display the variation of SS vs. FPR for different values of the chosen variables, were finally used. For each patient, the best predictor was defined as the set of parameters whose performance was closer (Euclidean distance) to the optimal (SS=100%, 0 FP/h).

C. Random Predictor

To evaluate the statistical significance of the predictor, we compared our results with a random predictor based on a Poisson process, that produces alarms independently of any EEG information, providing a good coarse estimation of the algorithm predictive power [8]. Assuming a random alarm generation, the probability to predict at least k from a total of K seizures is given by a binomial distribution [8]:

$$P_{binom}\{k;K;P\} = \sum_{j\geq k}\binom{K}{j}P^j(1-P)^{K-j} \quad (5)$$

where P indicates the probability (Poisson) for a single alarm to occur during some interval of time. Furthermore, for the optimization of prediction methods, several parameters are optimized retrospectively. This multiple testing problem must be taken into account when assessing statistical significance. If the proposed predictor optimizes a number d of independent parameters, the probability of the random predictor is affected as follows [8]:

$$P_{binom,d}\{k;K;P\} = 1-\left(1-\sum_{j\geq k}\binom{K}{j}P^j(1-P)^{K-j}\right)^d \quad (6)$$

Considering the bounds of d, under the assumptions that all the free parameters are dependent or independent, critical sensibility levels $\sigma_{rand,d}$ can be established, for $d=1$ (σ_{low}) and for $d=d_{max}$, the total number of free parameters (σ_{up}).

$$\sigma_{rand,d} = \frac{1}{K}\cdot max_k\left(P_{binom,d}\{k;K;P\}>\alpha\right)\cdot 100\% \quad (7)$$

where α represents the significance level of the predictor ($\alpha = 0.01$ in this case) [8]. Therefore, the sensitivity SS of our predictor must be above σ_{low} to be useful, and above σ_{up} to be superior to the random one. In the case that SS lies

within the interval $[\sigma_{low}, \sigma_{up}]$, it cannot be assumed as a definitely superior predictor [8]. In our evaluation, $d_{max} = 144$ free parameters: 3 possible preictal times, 4 phase-amplitude pairs $(\varphi_{low}, A_{high})$, and 12 possible intervals $[\varphi_{coupl1}, \varphi_{coupl2}]$.

III. Results

Fig. 2 shows an example of our analysis for a representative patient (ID: 13). It can be observed that, for a majority of contacts, the phase of coupling was stable for several hours during the interical state ($\sim -0.5rad$) and that preictal deviations were seen, at multiple locations within or outside the focus, tens of minutes before the seizures. From the alarms defined when the number of contacts with a specific coupling phase was over a critical threshold, Fig. 3 shows in the ROC curve (for the same patient), the performance for different values of the chosen variables. From all 15 investigated seizures, the optimal performances were SS=100% and FPR=0.18FP/h, suggesting that all seizures were predicted correctly with a low false prediction rate. To decide on the statistical significance of these values, we compared our results with the performance of an unspecific random predictor. In this patient, the optimal points, corresponding to the best prediction on the real data, exceeded the critical values of the random predictor, suggesting that our predictor was better than a random one.

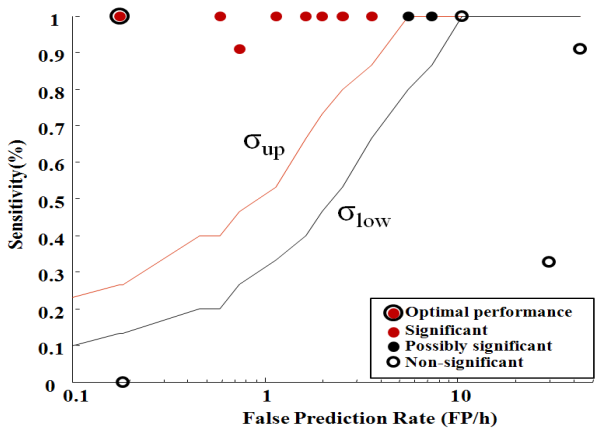

Fig. 3. ROC curves analysis. SS vs. FPR for different parameters. Continuous lines are the critical performance of the random predictor, so that points above them are significant. The best performance is selected as the point closest to (0,1).

For the group of 20 patients, Table I shows the overall performances of our method. In 10/20 of cases, significant results (above σ_{up}) were observed in comparison to the random predictor. For these significant patients, an average sensitivity of 98.9% and FPR of 1.84FP/h were reached. As expected by the heterogeneity of epileptic disorders investigated in our group of pharmaco-resistant epilepsy, we found that optimal cross-frequency coupling bands varied for individual patients with any relevant preference: $LG-\delta$:30%; $LG-\theta$:30%; $HG-\delta$:20%; and $HG-\theta$:20%. Finally, different values of preictal window lengths were tested and we found that an optimal duration of 10 minutes could be identified for the patients whose predictions had significant performances (Table I).

IV. Discussion

Our study suggests that a measure of brain excitability identified by the coupling between low-frequency phase and high-frequency amplitude could predict seizures on unselected, continuous and long-term recordings of patients with pharmaco-resistant epilepsy. In contrast to other studies of seizure prediction methods [1], we compared our seizure prediction performances to a random predictor, to judge its statistical significance. For the 50% of the patients whose prediction had significant performances, the sensitivity and FPR may be within the range of useful clinical values. In particular, we have found significant results with just a 10-minute-long prediction horizon. In general, algorithms that use short prediction horizons usually produce low sensitivity less than 60% with false-positive rates around 1 per hour [9]. Nevertheless, this analysis is not equivalent to an evaluation of the prospective predictive power of the algorithm, as it combines the information from the learning data and advance prediction. Despite this, our evaluation gives a good orientation for the expected significance of the results. In the future, it may be relevant to investigate how selecting channels at different location relative to the seizure onset zone could affect seizure prediction performances. Also, it would be important to adapt our strategy to scalp EEG, where myogenic artefacts constitute a serious obstacle for investigation of high frequency oscillations, thus making the design of a practical warning system feasible.

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