BISPECTRAL ANALYSIS OF GLOBUS PALLIDUS LOCAL FIELD POTENTIALS IN DYSTONIA AND PARKINSON'S DISEASE

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Abstract: Bispectral analysis has been widely used in the last years to understand the interrelations between different rhythms in bioelectrical activity. Compound nuclear activity (Local Field Potentials, LFPs) in human Basal Ganglia can now be recorded and analyzed thanks to the unique opportunity given by the electrodes implanted for Deep Brain Stimulation (DBS). Power spectral analysis of LFPs revealed that spectral components differ between Parkinson's Disease (PD) and dystonia. In this work we applied the bispectral analysis in order to investigate possible nonlinear interaction between rhythms at different frequencies and eventual effects over the spectral profiles in PD and Dystonia. We evaluated the bispectrum and the bicoherence of signals recorded from one patient with idiopatic PD and one with dystonia, both implanted in the Globus Pallidus internus with DBS electrodes. The bispectral analysis in PD showed the existence of a complex pattern of nonlinear interactions, meaning that the rhythms characterizing the power spectrum are synchronized. On the contrary, bicoherence analysis in the dystonic patient revealed a substantial independence of the characteristic spectral components. In conclusion, the application of bispectral analysis revealed that not only the spectral power but also the interrelations between rhythms are different between the two conditions.

Introduction

Bispectral analysis has been widely used in the last years to understand the interrelations between different rhythms in bioelectrical activity. Results were obtained on cortical EEG signal and on heart rate variability [1], [2], [3]. Compound nuclear activity (Local Field Potentials, LFPs) in human Basal Ganglia (BG) can now be recorded and analyzed thanks to the unique opportunity given by the electrodes implanted for Deep Brain Stimulation (DBS). LFPs represent the synchronous activity of wide neuronal populations, which is different from the firing rate of the single neuron [4]. Studies on the internal Globus Pallidus (GPi) LFPs revealed the substantial oscillatory nature of this structure [5], [6]. Power spectral analysis on GPi LFPs evidenced the existence of specific rhythms that characterize the oscillatory activity in different conditions and different pathologies. Particularly, it has been observed that the spectral components differ between Parkinson's Disease (PD) and dystonia. Thanks to recent studies on LFPs, the classical BG model, based on single neuron firing rates, is enriched by the complementary information processing provided by multiple LFPs rhythms distributed across large populations of neurons. In the light of this new scenario, the thalamo-cortico-basal information processing seems to be more complex and the hypothesis of the presence of nonlinearities and synchronizations between rhythms seems to be more likely. Power spectral analysis does not provide information on the phase relations and nonlinear interactions between spectral components: the power spectrum contains, in fact, the same information as the autocorrelation sequence, in which the phase relations are suppressed. Such an information is, on the other hand, provided by higher-order spectra defined in terms of higher order cumulants. In this work we applied the bispectral analysis (third-order analysis) in order to investigate possible nonlinear interactions between rhythms at different frequencies and eventual effects over the spectral profiles in PD and Dystonia.

Methods and data analysis

Higher-order spectra are defined in terms of higher-order statistics, as well as the power spectrum is defined in terms of autocorrelation sequence. LFPs can be statistically interpreted as stationary and ergodic random processes, at least in time windows of a few seconds. Therefore, cumulants, instead of moments, are used in the definition of the higher order spectra [7], [8]. All the definitions will be given under the assumption of zero-mean. The *Bispectrum,* $B(f_1,f_2)$, is defined as the two-dimensional Fourier Transform (FT) of the third order cumulant sequence (1).

$$B(f_1, f_2) = \sum_{m=-\infty}^{+\infty} \sum_{n=-\infty}^{+\infty} R(m,n) e^{-j2\pi f_1 m} e^{-j2\pi f_2 n} \quad (1)$$

$$R(m,n) = E[X(t)X(t+m)X(t+n)]$$

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where f_1 and f_2 are the frequencies of the spectral components, $R(m,n)$ is the third-order cumulant as a function of the corresponding time lags m and n, and $X(t)$ is the signal. The bispectrum $B(\omega_1,\omega_2)$ is generally complex (it has magnitude and phase), it is doubly periodic with period of 2π (it is 2π periodic on ω_1 and on ω_2) and it inherits the symmetry properties of the cumulant sequence. The knowledge of the bispectrum in the triangular Region [$\omega_2<=\pi$, $\omega_1>=\omega_2$, $\omega_1+\omega_2<=\pi$] is sufficient for a complete description of the bispectrum [7], [8]. The bispectrum, as well as the cross-spectrum in the second-order statistic, can be normalized. The normalized bispectrum is called *bicoherence* and it is obtained from the bispectrum, divided by the product of the autospectra (2).

$$Bic(\omega_1,\omega_2) = \frac{B(\omega_1,\omega_2)}{\sqrt{P(\omega_1)P(\omega_2)P(\omega_1+\omega_2)}} \quad (2)$$

where $B(\omega_1,\omega_2)$ and $P(\omega)$ are respectively the bispectrum and the power spectrum of the signal [7], [8].

The signals analyzed in this study were recorded from one patient with idiopatic PD and one with dystonia, two days after DBS surgery, while the wires from the macroelectrodes were still externalized, before the connection to the subcutaneous high-frequency stimulator. Patients were bilaterally implanted in the GPi with macroelectrodes for DBS (model 3389 Medtronic, Minneapolis, USA). The 3389 Medtronic electrode has four cylindrical contacts (2.7 mm of diameter, 1.5 mm of length, 2 mm spaced center to center) called 0-1-2-3, beginning from the more caudal. According to intraoperative and postoperative tests, contact 1 was verified to be within GPi. The procedures for the localization of the DBS electrodes are described in detail in [9].

LFPs signal was recorded from bipolar derivation (contacts 1 – 2), filtered in the 2-1000 Hz band, sampled at 2500 Hz and digitized with 12 quantization levels with 5 V range. The digitized signal was stored on a personal computer and displayed by the Signal Software (Signal Software, version 1.80, Cambridge Electronic Design). All the data analysis was conducted off-line with the Matlab software (version 6.5, The Mathworks, Natik, MA, USA) with custom-written programs.

As a preprocessing step, LFPs were normalized by subtracting the mean and dividing by the standard deviation of the 600-1000 Hz band-pass filtered signals. This procedure imposes the same background noise to all the recordings, reducing the variability [10] . Data were digitally filtered below 40 Hz and resampled at 125 samples per second. 60 seconds of rest recording were considered. Frequencies below 40 Hz were divided in the three bands that characterize the oscillatory activity pattern in the GPi [5], [6]: the low-frequencies (2 -7 Hz), the low-beta (13-17 Hz), and the high-beta (20-35 Hz). Nonlinear interactions between two of these rhythms, f_1 and f_2, and the possible generation of spurious harmonics at f_1+f_2 by quadratic coupling were assessed in the bispectrum by components at the intersection (f_1, f_2) in the bispectral plane. The high beta frequencies were not considered in this composition because they can generate harmonics above the considered band width of 40 Hz. Therefore, we defined three "Regions Of Interest" (ROIs) : Region 1: (2-7 Hz, 2-7 Hz), Region 2: (13-17 Hz, 13-17 Hz), Region 3: (2-7 Hz, 13-17 Hz), as represented in Figure 1.

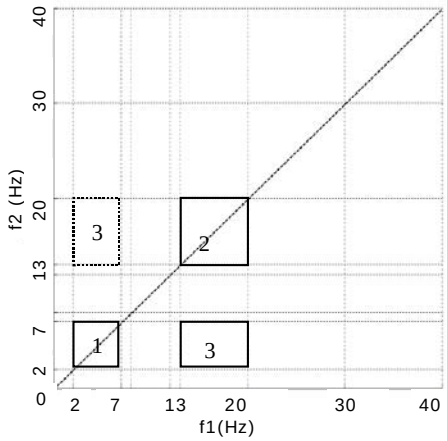

Figure 1: Regions Of Interest (ROIs) represented in the bispectral plane. The diagonal represents a symmetry axis: ROIs in the lower part of the plane (solid squares) are the same as ROIs in the upper part of the plane (dotted squares). ROIs on the diagonal are symmetrical, too. ROI 1 = [2-7 Hz, 2-7 Hz]; ROI 2 = [13-20 Hz, 13-20 Hz]; ROI 3 = [2-7 Hz, 13-20 Hz].

Spectra, bispectra and bicoherences were estimated via the non parametric approach based on the Discrete Fourier Transform, with a frequency resolution of 0.98 Hz. Spectra were calculated using Welch's averaged, modified periodogram method. The spectral power of each band (f_1-f_2) defined above was calculated as in (3)

$$P_{(f1-f2)} = \int_{f1}^{f2} PSD(f)df \quad (3)$$

and normalized dividing by the total power below 40 Hz. The bispectrum and the bicoherence were estimated with the direct nonparametric approach: signals were divided into records of 128 samples and the mean was subtracted; DFT coefficients of each record were generated; the estimated bispectrum and the estimated bicoherence were calculated in each record and, then, averaged to obtain the estimated bispectrum and the estimated bicoherence of the whole signal. The bicoherence estimation, combining information from the bispectrum and the power spectrum, requires both the bispectrum and the power spectrum to be estimated from data. Hence, the bicoherence results from the combination of two different estimation methods, third order statistic and second order statistic. Therefore, even if the theoretic bicoherence of a process is bound to the [0,1] interval, this is not true in the estimation from data

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[3]. The bicoherence of signals with relatively low signal to noise ratio typically includes many spurious peak due to the noise. As a result, the 2-D map of the bicoherence usually contains many peaks that reflect both noise (spurious peaks) and nonlinear phase coupling (true peaks). The introduction of a threshold based on the statistical properties of the estimator can discriminates true peaks (over the threshold) from spurious peaks (below the threshold). The bicoherence estimate (squared modulus) has an asymptotical chi-squared distribution with $1/\sigma^2$ degrees of freedom, where σ^2 is defined as in (4)

$$\sigma^2 = C\frac{N_0^2}{N * f_s} \qquad (4)$$

where N_0 is the number of samples per segment (i.e. 128), f_s is the sampling frequency (i.e. 125 Hz), N is the total number of samples (60 seconds with 125 samples per second) [11], [12]. The threshold level for the significant bicoherence was calculated as the 95% confidence interval of the chi-squared distribution, given by (5).

$$\left|\hat{Bic}(\omega_1,\omega_2)\right|^2 \geq 6\sigma^2 \qquad (5)$$

The presence of significant bicoherence peaks was tested in each ROI for all individual nuclei. Around each significant peak of bicoherence (f_1',f_2'), a squared subregion (f_1'±2 Hz, f_2'±2 Hz), R_n, was considered for the evaluation of the volume of the bispectrum , according to the equation (6):

$$BspP(R_n) = \iint_{R_n} B(f_1, f_2)df \qquad (6)$$

where R_n is the ROI; $A(R_n)$ is the area of the ROI (Hz^2) and $B(f_1,f_2)$ is the bispectrum at the frequencies (f_1,f_2).

Results

According to [6], the spectral profile of the dystonic subject had a higher percentage spectral power in the Low Frequencies band than in the beta band (low beta+high beta); on the contrary, the PD patient presents a lower percentage spectral power in the Low Frequencies than in the beta band (low beta+high beta).

Table 1: percentage distribution of the spectral power among frequency bands in PD patient and in the dystonic patient

PATIENT	LOW FREQUENCIES	LOW BETA	HIGH BETA
PD	0.2824	0.1725	0.2377
Dystonia	0.5739	0.1082	0.1265

The bispectral analysis in the PD patient showed, in addition, the existence of a bicoherence peak in Region 1 (6Hz, 6Hz), in Region 2 (13Hz, 13Hz), and in Region 3 (6Hz, 3 Hz), meaning that both the low frequencies and the low beta generated spurious harmonics (Figure 2a). On the contrary, bicoherence analysis in the dystonic patient revealed a significant peak only in Region 1 (6 Hz, 6 Hz), with a lower bispectral power , which could justify a spurious contribution only within the low-frequencies band. No significant activity was found in Region 2 and Region 3 (Figure 2b). Moreover, the evaluation of bispectral parameters showed that the PD patient presented an higher bispectral volume in all the ROIs and a higher bispectral total volume in the area (0-40 Hz, 0-40 Hz), indicating an higher degree of nonlinear interactions between the rhythms (Table 2). Note that nonlinear interactions cause the spectrum of PD patient to have a power spread all over the frequency axis, without well-defined rhythms. On the contrary, in the dystonic patient it is possible to well distinguish the peaks relative to the low frequencies and the high beta activities.

Table 2 : Bispectral values in ROI 1, ROI 2, ROI 3 and the total bispectral volume in the (0-40 Hz, 0-40 Hz) area

PATIENT	ROI 1	ROI 2	ROI 3	TOTAL VOLUME
PD	94.0603	9.2882	29.0038	552.5144
Dystonia	13.0682	0.6645	4.7018	69.0289

Discussion and conclusions

Our results are in agreement with previous findings on GPi LFPs in PD and dystonia, but the application of bispectral analysis based on bicoherence examination and bispectral power evaluation, revealed that not only the spectral power but also the interrelations between rhythms are different between the two conditions. In particular, thanks to the application of the bispectral analysis it is possible to assess that the rhythms expressed in the parkinsonian GPi are characterized by a large amount of nonlinear interactions, while in the dystonic GPi the rhythms are substantially independent.
Bispectral analysis was first applied to neural signals in the early seventies, in order to study the interactions between rhythms detected by scalp EEG recordings [1], [2]. Bispectral measures became widely employed in clinical EEG literature to monitor the depth of anesthesia and other intra-operative parameters [13]. A number of studies also applied bispectral analysis to investigate the presence of non-linear interactions between EEG rhythms over the sensorimotor cortex. Our results suggest that also in the case of deep EEG signal bispectral and bicoherence analysis can evidence characteristics able to undercover the basic mechanisms of information processing among neural networks. Moreover, the investigation of nonlinear interactions can help in the correct interpretation of the power spectrum. As in the case examined, the oscillatory pattern showed by the power spectrum contains also the activity due to the presence of harmonics and,

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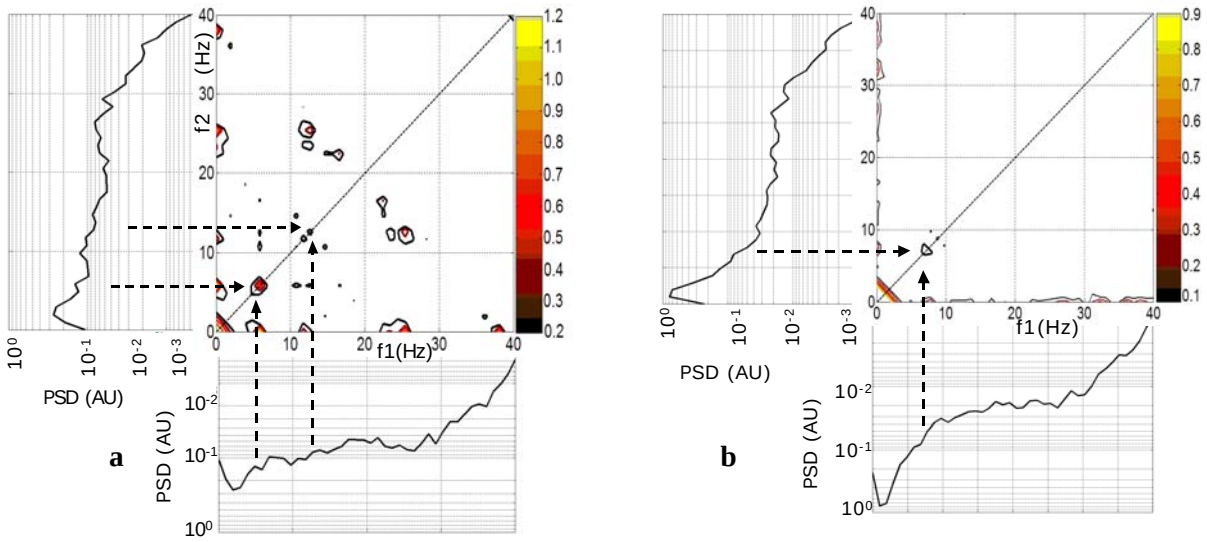

Figure 2 : Bicoherence in the two nuclei analyzed. (a) PD patient. (b) Dystonic patient. The central 2D plot shows the bicoherence in the plane (f_1, f_2). The level-lines in the plot represent significant bicoherence values color coded as indicated in the color-bar on the right. The power spectrum of the signal is presented in the left plot and in the lower plot in correspondence to the two frequency axes. The diagonal in the central plot defines the two regions of symmetry of the bicoherence. The dashed arrows indicate the oscillatory components that are coupled.

therefore, the definition of the rhythms that characterize the nucleus functions in the condition examined becomes difficult. The knowledge of the bispectrum permit, if not a real quantification, at least a qualitative distinction between the activity due to synchronizations and the independent activity.

The bispectral parameters extraction revealed to be a useful tool to quantify the bispectral activity of the signal: considering that the bicoherence amplitude did not lie between 0 and 1 and that the obtainable value depends on sample size and other computational details, the idea here was to use the presence of a bicoherence peak as a marker of synchronization and the bispectral power as a quantity to compare signals from different nuclei.

In conclusion, the bispectral and bicoherence analysis permitted to quantify the degree of synchronization between different rhythms, providing new elements useful to extend the current pathophysiological model of the human basal ganglia.

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