# School of Biomedical Engineering, Science, and Health Systems

# Interaction Between Rhythms in the Human Basal Ganglia: Application of Bispectral Analysis to Local Field Potentials

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***Abstract*—The application of deep brain stimulation (DBS) for the treatment of Parkinson's disease offered a direct "insight" into the human electrical activity in subcortical structures. The analysis of the oscillatory activity [local field potentials (LFPs)] disclosed the importance of rhythms and of interactions between rhythms in the human basal ganglia information processing. The aim of this study was to investigate the existence of possible nonlinear interactions between LFP rhythms characterizing the output structure of the basal ganglia, the globus pallidus internus, by means of bispectral analysis. The results of this study disclosed that the rhythms expressed in the globus pallidus internus of the untreated parkinsonian patient are not independent and, in particular, the low-beta (13–20 Hz) band generates harmonics that are included in the high-beta (20–35 Hz) band. Conversely, in the dystonic globus pallidus, as well as in the parkinsonian globus pallidus after dopaminergic medication (i.e., in the more "normal" condition), the rhythms are substantially independent and characterized by a strong activity in the low-frequency band that generates a second harmonic (4–14 Hz), mostly included in the same band. The interactions between rhythms in the human globus pallidus are therefore different in different pathologies and in different patient's states. The interpretation of these interactions is likely critical for fully understanding the role of LFP rhythms in the pathophysiology of human basal ganglia.**

***Index Terms*—Basal ganglia, bispectral analysis, deep brain stimulation, dystonia, Parkinson's disease.**

## I. Introduction

DEEP BRAIN STIMULATION (DBS) is an established and widely applied surgical therapy for Parkinson's disease (PD), dystonia, and other neurological disorders [1]–[7]. Electrodes for DBS are implanted in structures hitherto inaccessible for studies in humans and *in vivo*. The introduction of DBS offered a direct "insight" into the human electrical activity in sub-cortical structures [8]. In particular, the aggregate presynaptic and postsynaptic activity of large populations of neurons can be detected, in the form of local field potentials (LFPs), through the electrodes positioned in the DBS target structure [9]–[16]. LFP studies revealed the "oscillatory nature of human basal ganglia activity" [8], disclosing the importance of the "oscillation mode," in addition to the "single-spike mode" for information sharing in the cortico-basal ganglia-thalamo-cortical network [17].

Oscillations in the basal ganglia were disclosed to range in a wide interval, from low frequencies (below 7 Hz), to frequencies in the beta band (13–35 Hz) [8], [18]–[45], up to high frequencies, around 70Hz [23], [26], [46] and around 300 Hz [46], [47]. In line with the previous experience on electroencephalographic signals, LFPs were investigated with several methodological approaches and in different patient's conditions to establish the functional role of subcortical oscillations. LFP rhythms are modulated by dopamine intake, by voluntary movement execution and imagination, and are related to the patient's clinical and motor state [8], [18]–[20], [23]–[26], [28]–[30], [35]–[39], [41], [42], [44]–[53]. Different pathologies are characterized by different LFP patterns: interestingly, the LFP pattern in PD and dystonia can be characterized by the balance between the oscillations in the low-frequency and in the beta band (low-frequencies/beta balance), which is shifted to the beta band in untreated PD, whereas the low-frequencies are dominant in dystonia as well as in treated PD [29], [41].

Also, LFP recordings are intriguingly connected with the still controversial DBS mechanism of action: the clinical efficacy of DBS is suggested to be related to the modulation of a pathological network activity [54]–[56]. In fact, the beta LFP rhythm transiently decreases during short trains of DBS [22], [57]. Conversely, the low frequency ($<7$ Hz) LFP rhythm increases immediately after long trains of DBS, when the clinical efficacy is still observable [51]. The observation of LFP rhythms at very-high frequencies (300 Hz), which are around twice the stimulation frequency, could also support the hypothesis of a subharmonic driving action of the DBS on the network activity [47], [58].

The analysis of LFPs therefore pointed out the physiological and pathophysiological role of these oscillations, turning the attention to the network level to complement observations at the cellular level. Information processing in the basal ganglia-thalamo cortical loop could be mediated not only by the classical

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channels of firing rate at the cellular level [17], [59], [60], but also by new channels of oscillatory activity operating at different frequencies at the network level [39], [61]. This increasing complexity of the basal ganglia model results in the need of investigating the reciprocal interaction between oscillatory information channels at the network level, i.e., to study nonlinear coupling and phase synchronization between LFP rhythms.

The reciprocal interactions between LFPs rhythms were already described, through the application of bispectral analysis, in the subthalamic area in PD, pointing out the nonlinear behavior of basal ganglia oscillators [38]. This approach revealed that the loss of segregation typical of the dopamine depleted condition can be extended from the cellular level to the network level. After restoration of more normal dopamine levels by levodopa administration, the oscillatory information channels revert to functional independence [38].

The interaction between rhythms seems to contribute to information processing in the human basal ganglia. The study of these interactions should therefore be extended to other basal ganglia structures and to other movement disorders. To this end, in this study we applied bispectral analysis to investigate the existence of possible nonlinear interactions between LFP rhythms characterizing the output structure of the basal ganglia, the globus pallidus internus (GPi), in dystonia. The results were then compared to 1) those obtained in a patient affected by PD with a double implant in the GPi and in the subthalamic nucleus (STN) and 2) those obtainted in the STN in a group of patients affected by PD and previously reported [38].

## II. Methods

### A. Bispectral Analysis

Nonlinear interactions and phase synchronizations between the rhythms characterizing a system can be detected by means of bispectral analysis. When the process generating a signal is Gaussian and linear, the power spectrum, that is the Fourier transform (FT) of the second order statistic, can fully describe the signal and the characterizing rhythms are independent. In the power spectrum, phase relations between rhythms are completely lost. Conversely, the bispectrum does contain such information and it is particularly useful in the detection of phase-locking phenomena [62]–[65]. The bispectrum is a particular case of higher-order spectrum and it is defined as the 2-D FT of the third-order cumulant, which equals the third order moment if the considered process is zero-mean

$$R(m,n) = E\left[x(t)x(t+m)x(t+n)\right]$$
$$B(f_1,f_2) = \sum_{m=-\infty}^{+\infty}\sum_{n=-\infty}^{+\infty} R(m,n)e^{-j2\pi f_1 m}e^{-j2\pi f_2 n} \quad (1)$$

where $R(m,n)$ is the third-order cumulant (= third-order moment) as a function of the corresponding time lags $m$ and $n$, $\mathrm{x}(t)$ is the signal, i.e., a zero-mean stationary random process, $B$ is the bispectrum, and $f_1$ and $f_2$ are the frequencies of the spectral components.

The bispectrum examines whether the rhythms at frequencies $f_1$, $f_2$ and $f_1+f_2$ are phase coupled, so that the $f_1+f_2$ rhythm is generated by the nonlinear relation between $f_1$ and $f_2$. In particular, when $f_1 = f_2$ it detects a harmonic relation between a rhythm at $f_1$ and the rhythm at the double of $f_1$ [66].

The bispectrum can be normalized, according to the definition proposed by Mendel (1991), to reduce the effect of the spectral power on bispectral peaks. The normalized bispectrum is called bicoherence

$$Bic(f_1,f_2) = \frac{B(f_1,f_2)}{\sqrt{P(f_1)P(f_2)P(f_1+f_2)}} \quad (2)$$

where $B(f_1,f_2)$ is the bispectrum at frequencies $(f_1,f_2)$ and $P(f_\mathrm{i})$ is the power spectrum at frequency $f_\mathrm{i}$ [67].

### B. Experimental Procedures

We recorded LFPs in eight GPi from four patients (two males and two females) affected by dystonia, and in one GPi and one STN from a patient affected by PD. All the dystonic patients underwent DBS surgery for the bilateral implantation of stimulating electrodes in the GPi (model 3389 Medtronic Inc., Minneapolis, MN). The PD patient, whose case was previously described [29], was implanted both in the GPi and in the STN. All of them were studied after informed consent and local ethical committee approval. The DBS target structure was identified by direct visualization through a CT-MRI fusion-based technique before surgery, as extensively reported elsewhere [68], [69]. The implanted 3389 Medtronic electrode has four cylindrical contacts (1.27 mm in diameter, 1.5 mm in length, placed 2 mm apart, center to center) denominated 0-1-2-3, beginning from the more caudal contact.

LFPs were recorded two days after surgery through the implanted DBS electrodes, still externalised before the connection with the subcutaneous high-frequency stimulator. All patients were recorded bilaterally. Recordings were performed at rest for 2–3 min in all nuclei. The PD patient was studied both before ("off" dopaminergic condition) and after ("on" dopaminergic condition) the administration of levodopa therapy (125 mg of oral fast-acting levodopa—Madopar Dispersibile—Roche, Monza, MI, Italy) following the experimental protocol previously used in a group of PD patients with electrodes implanted in the STN [38].

Signals were preamplified, filtered (band pass 2–1000 Hz), and differentially amplified (100 000x) with an analogical amplifier (Signal Conditioner Cambridge 1902, Cambridge Electronic Design, Cambridge, U.K.). The output signal was digitized (Cambridge Micro 1402, Cambridge Electronic Design, Cambridge, U.K.), with sampling rate 2500 Hz and 12 bit quantization with 5 V range. All further analysis was conducted offline with the Matlab software (version 6.5, The Mathworks, Natik, MA). Each recording was normalized by subtracting the mean and dividing by the standard deviation of the 600–1000 Hz bandpass filtered signal, in order to impose the same background noise to all recordings [38], [39], [47]. Signals were then digitally band passed (2–45 Hz) and down-sampled at 125 Hz.

### C. Bispectrum and Bicoherence Estimation

The power spectrum, the bispectrum and the bicoherence were estimated through the direct nonparametric method [63],

[64]. As fully described in Huber *et al.* (1971) and Kim and Powers (1979), to obtain consistent estimators, the bispectrum obtained directly from data should be averaged. A first possibility is to average the bispectrum obtained with the entire data sample in the frequency domain; another possibility is to average over records, therefore dividing the signal in K records of length N; finally, the two methods can be combined. In our procedure we chose to average bispectrum over records, without averaging in the bispectrum domain.

Our data sample was composed by 60 s recordings with a sampling frequency of 125 samples/second ($N_{\text{tot}} = 7500$). Data were divided into 58 records of 128 points by a rectangular window, thereby not introducing tapering procedures, with no overlap. After removing the sample mean, the discrete time Fourier transform (DFT) coefficients were calculated in each record

$$Y_i(f) = \sum_{t=0}^{N-1} x_i(t) e^{-j2\pi \frac{f}{N} t} \quad f = 1, \ldots, \frac{N}{2} \tag{3}$$

where $N$ is the number of samples (128) in the $i$th record, $x_i(t)$ is the signal, and $Y_i(f)$ is the DFT coefficient. Then, the power spectrum and the bispectrum of the $i$th record were estimated in their principal domains as

$$P_i(f) = Y_i(f) Y_i*(f) \quad f = 1, \ldots, \frac{N}{2} \tag{4}$$

$$\begin{aligned} B_i(f_1, f_2) &= Y_i(f_1) Y_i(f_2) Y_i*(f_1 + f_2) \\ 0 &\le f_1 \le \frac{N}{2} \\ 0 &\le f_2 \le f_1 \\ 2f_1 + f_2 &\le N. \end{aligned} \tag{5}$$

The power spectrum and the bispectrum were then averaged over the records to obtain consistent estimators

$$\begin{aligned} \hat{P}(f) &= \frac{1}{K} \sum_{i=1}^{K} P_i(f) \\ \hat{B}(f_1, f_2) &= \frac{1}{K} \sum_{i=1}^{K} B_i(f_1, f_2) \end{aligned} \tag{6}$$

where $K$ is the number of records (58).

This bispectral estimate is asymptotically unbiased [70] with variance [63]

$$\text{var}\left(\hat{B}(f_1, f_2)\right) = \frac{N^2}{N_{\text{tot}} f_{\text{sampling}}} P(f_1) P(f_2) P(f_1 + f_2) \tag{7}$$

where $P(f)$ is the real power spectrum of the signal, $N$ is the number of samples per record (128), $N_{\text{tot}}$ is the total length of the sample (7500 samples) and $f_{\text{sampling}}$ was 125 Hz.

Bicoherence was then calculated according to [63], [71] as

$$bi\hat{c}(f_1, f_2) = \frac{\hat{B}(f_1, f_2)}{\left(\hat{P}(f_1) \hat{P}(f_2) \hat{P}(f_1 + f_2)\right)^{1/2}} \tag{8}$$

In a first order approximation it is possible to neglect the variance of the bicoherence denominator [63], thereby obtaining

$$\text{var}\left(bi\hat{c}(f_1, f_2)\right) \cong \frac{N_0^2}{N_{\text{tot}} f_{\text{sampling}}} = \frac{128^2}{7500 * 125} = 0.0175. \tag{9}$$

A further correction must be added in case of tapering and sample overlapping, but we did not apply any of these procedures. Also, variance on the diagonal and on the border ($2j + k = N$) are doubled. Single variances can be considered as independent variables with a normal distribution [70]. Consequently, the magnitude squared bicoherence is approximately chi-square with 2 degrees-of-freedom with an expected value

$$E\left(\left|bi\hat{c}(f_1, f_2)\right|^2\right) = 2\sigma^2 = \frac{N_0^2}{N_{\text{tot}} f_{\text{sampling}}} = 0.0175 \tag{10}$$

Following the chi-square distribution, the probability that

$$\left|bi\hat{c}(f_1, f_2)\right|^2 \ge 6\sigma^2 \tag{11}$$

occurs by chance is 0.05 and the probability that

$$\left|bi\hat{c}(f_1, f_2)\right|^2 \ge 9.2\sigma^2 \tag{12}$$

occurs by chance is 0.01. Therefore, the statistic significance of the magnitude squared bicoherence estimate could be calculated according to the chi-square distribution. The magnitude squared bicoherence could be used for testing whether the bispectrum differs from zero [63].

As noted by Elgar and Guza (1988) [72] the statistics of magnitude squared bicoherence is independent of whether it is obtained by averaging over short records or averaging in the frequency domain within long records.

We set the significance threshold for nonzero magnitude squared bicoherence to $p = 0.05$ conservatively considering as all the elements were on the diagonal (i.e., the variance was doubled). Therefore

$$\begin{aligned} \left|bi\hat{c}(f_1, f_2)\right|^2 &\ge 6\sigma^2 \\ 6\sigma^2 &= 0.1049 \end{aligned} \tag{13}$$

were considered significantly deviating from 0.

### *D. Data Analysis*

Consistently with previous works, data were analysed in the classical EEG frequency range (below 45 Hz), focusing particularly on the oscillatory activity in three bands, namely low frequencies (2–7 Hz), low-beta (13–20 Hz), and high-beta (20–35 Hz) [29], [41]. Accordingly, we defined three regions of interest (ROIs) in the bispectral domain, to detect possible nonlinear interactions between these rhythms (Fig. 1): ROI 1 = [2 – 7 Hz, 2 – 7 Hz], ROI 2 = [13 – 20 Hz, 13 – 20 Hz], ROI 3 = [2 – 7 Hz, 13 – 20 Hz]. To quantify the oscillatory activity in LFPs, and to evaluate the low-frequencies/beta balance,

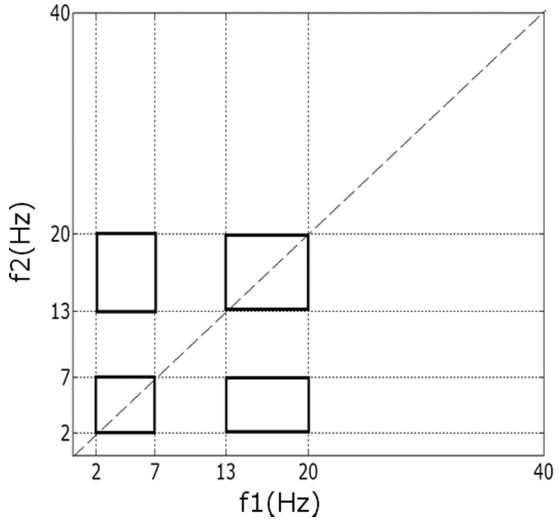


Fig. 1. ROIs represented in the bispectral plane. Diagonal represents a symmetry axis: ROIs in the lower part of the plane are the same as ROIs in the upper part of the plane. ROIs on the diagonal are symmetrical, too. $\mathrm{ROI}\ 1 = [2-7\ \mathrm{Hz}, 2-7\ \mathrm{Hz}]$; $\mathrm{ROI}\ 2 = [13-20\ \mathrm{Hz}, 13-20\ \mathrm{Hz}]$; $\mathrm{ROI}\ 3 = [8-12\ \mathrm{Hz}, 13-20\ \mathrm{Hz}]$.

we calculated the mean spectral power within each frequency band

$$SpPwr = \frac{1}{\Delta x} \sum_{j \in \mathrm{band}} \hat{P}(j) \tag{14}$$

where $\Delta x$ is the length of the frequency band. To quantify the interactions between different rhythms we used two measures: the significant squared modulus of the bicoherence (simply called throughout the text bicoherence) and the bispectral power, calculated as the mean of the estimated bispectrum over a ROI (simply called throughout the text bispectral power)

$$BspPwr = \frac{1}{\Delta x \Delta y} \sum_{j,k \in \mathrm{ROI}_i} \left| \hat{B}(j,k) \right| \tag{15}$$

where $\Delta x \Delta y$ is the area of the ROI. Because ROIs on the diagonal (ROI 1 and ROI 2) were on one of the symmetry axes of the principal domain, the bispectral power in ROI 3 was doubled. Bispectral power and bicoherence provide complementary indices: whereas the bicoherence was applied for analysis at the single nucleus level (i.e., detecting the existence of a significant nonlinear interaction in a certain ROI), the bispectral power was used for analysis at the population level (i.e., comparing different nuclei) [38]. Bispectral power and bicoherence in ROI 1 represent the generation of a second harmonic oscillation of the low-frequency rhythm. Similarly, bispectral power and bicoherence in ROI 2 represent the generation of a second harmonic oscillation of the low-beta rhythm, that mostly lies in the high-beta interval. Bispectral power or bicoherence in ROI 3 represent a nonlinear interaction between the low-frequency and the low-beta rhythms, generating an oscillation at the sum of the two. ROIs corresponding to the high-beta rhythm were not considered, because the generated harmonics would be within the range of the line noise (50 Hz).

We evaluated LFPs in 8 GPi from four patients affected by dystonia, 1 GPi and 1 STN from one patient affected by PD with a double DBS electrodes' implant. Because only one patient affected by PD was analyzed, the results from this patient were compared with those obtained in a general PD population [38]. This control group was composed by LFPs recorded from 13 nuclei from nine patients affected by PD, obtained with the same protocol used for the PD patient here considered, and analyzed with the same estimating procedure [38]. As reported in the literature, single nuclei were considered as independent samples even though belonging to the same patient [19], [26], [28], [39], [47], [73]. Several reasons support this choice: first, different electrodes are implanted in the left and right nuclei and, therefore, different measures are obtained from the two structures; second, electrodes are not implanted symmetrically, but the target is functionally chosen during intraoperative recording and stimulation sessions; third, impedances can be different and, finally, the two nuclei behave differently especially because movement disorders often present lateralized features.

To compare data from the STN and the GPi of the PD patient here analyzed and the parkinsonian control group, we calculated the *Z*-score of bispectral power in each ROI considering the normal distribution of the control group

$$Z = \left| \frac{X - \mu}{\sigma} \right| \geq 1.64 \tag{16}$$

where *X* is the bispectral power in a certain ROI, $\mu$ is the mean and $\sigma$ is the standard deviation of the bispectral power in that ROI obtained in the control group. 1.64 is the *Z* level corresponding to $p < 0.05$. Normality of the parkinsonian control group was ensured through a Shapiro-Wilk test (STATISTICA, Stat Soft, Inc., Tulsa, OK) with $p < 0.05$ for rejecting normality. Also, to underline the effect of levodopa medication, we calculated the percentage change in each ROI before and after the administration of dopaminergic medication as

$$\frac{BspPwr_{\mathrm{AFTER}} - BspPwr_{\mathrm{BEFORE}}}{BspPwr_{\mathrm{BEFORE}}} \tag{17}$$

and compared it with percentage changes obtained in the control group.

Finally, we performed a two-way analysis of variance (ANOVA, STATISTICA, Stat Soft, Inc., Tulsa, OK) to compare results obtained in the dystonic population with those of the control parkinsonian population. The first main factor was the condition (factor "condition," three levels, PD OFF, PD ON, dystonia; independent measures) and the second main factor was the ROI (factor "ROI," 3 levels, ROI 1, ROI 2, ROI 3, repeated measures). To break down the interaction, a one-way ANOVA with least significant difference (LSD) post hoc test for multiple factor interactions ($p < 0.05$) was performed to compare the condition in each ROI.

## III. Results

### A. Dystonic Patients

Spectral analysis of GPi LFPs from dystonic patients at rest revealed power spectra dominated by the oscillatory activity below 7 Hz, in the low-frequency band, whereas activity in the

TABLE I
AVERAGE RESULTS OF SPECTRAL AND BISPECTRAL ANALYSIS

| | | Dystonia | Patient with PD | | | | | | PD population | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GPi (n=8) | STN | | | GPi | | | STN (n=13) | | |
| | | | Off | On | Delta % | Off | On | Delta % | Off | On | Delta % |
| SPECTRAL POWER | Low frequencies (2-7 Hz) | 0.211 (0.216) | 0.032 | 0.070 | 119.4 | 0.040 | 0.057 | 43.3 | 0.075 (0.053) | 0.370 (0.490) | 52.6 (10.2) |
| | Low beta (13-20 Hz) | 0.040 (0.036) | 0.069 | 0.0194 | -71.7 | 0.039 | 0.025 | -34.9 | 0.109 (0.113) | 0.015 (0.007) | -66.4 (32.7) |
| | High beta (20-35 Hz) | 0.022 (0.025) | 0.025 | 0.012 | -52.9 | 0.013 | 0.017 | 28.0 | 0.028 (0.019) | 0.022 (0.027) | -16.9 (65.0) |
| BISPECTRAL POWER | ROI 1 (2-7,2-7 Hz) | 4.576 (6.778) | 0.063 | 0.177 | 181.4 | 0.152 | 1.026 | 576.8 | 0.871 (1.426) | 11.956 (20.799) | 3637.8 (8422.7) |
| | ROI 2 (13-20,13-20 Hz) | 0.128 (0.181) | 0.245 | 0.031 | -87.5 | 0.0753 | 0.044 | -40.9 | 0.653 (0.841) | 0.040 (0.036) | -28.5 (204.3) |
| | ROI 3 (2-7,13-20 Hz) | 0.843 (1.263) | 0.151 | 0.039 | -73.9 | 0.091 | 0.039 | -57.3 | 0.627 (0.591) | 0.504 (0.625) | 168.8 (583.3) |

Spectral and bispectral power are expressed as the mean of the spectrum/bispectrum in the band/ROI considered (column 2). Four dystonic patients ($n = 8$ nuclei, mean (SD) values are reported in the table) were recorded in the GPi; one Parkinson's disease (PD) patient ($n = 1$ nucleus) was recorded both in the GPi and in the subthalamic nucleus (STN) without (Off) and with (On) dopaminergi medication; a general PD population of 13 STN was considered as control. In the column labeled "delta%" are reported the percentage changes in each band/ROI considered after dopaminergic medication.

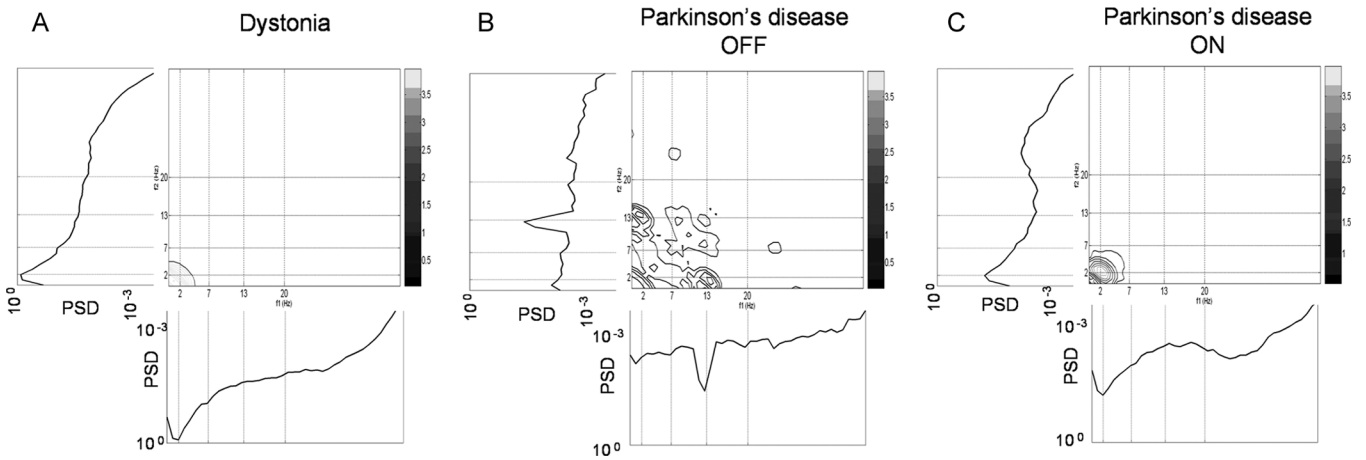


Fig. 2. Bispectral analysis of the GPi LFPs in dystonia (a) and Parkinson's disease (PD, Off levodopa condition: b; On levodopa condition: c). Panel A is the grand average of eight nuclei from four dystonic patients; panel B is the bispectrum of the PD patient in the off medication condition; panel C is the bispectrum of the LFPs in the nucleus of the PD patient recorded after levodopa medication. Each panel is organized in the same way: the central 2-D plot shows the bispectrum of the GPi LPF signal as a function of frequencies $f_1$ ($x$-axis in hertz) and $f_2$ ($y$-axis in hertz). Level-lines in the plot represent bispectrum values grey-scale coded as indicated in the bar on the right. Power spectrum of the signal is presented in the left plot and in the lower plot in correspondence to the two frequency axes. Diagonal in the central plot defines the two regions of symmetry of the bispectral plane.

beta band was consistently lower (Table I). Fig. 2(a) represents the average power spectrum of dystonic GPis analyzed at rest.

In addition, bispectral and bicoherence analysis [Fig. 2(a) and Fig. 3(a)] disclosed that the low-frequency band generates a second harmonic, without any other nonlinear interaction between rhythms: seven nuclei out of eight displayed a significant bicoherence peak in ROI 1, centred on ([mean $\pm$ SD] 2.44 $\pm$ 0.7 Hz, 2.44 $\pm$ 0.7 Hz); only one nucleus out of eight displayed a significant bicoherence peak in ROI 2, centred on (12.6953 Hz, 12.6953 Hz). Consistently, bispectral power [Fig. 2(a)] was concentrated in ROI 1, whereas in ROI 2 and ROI 3 the bispectral power was very low (Table I).

### *B. PD Patient With STN and GPi Electrode Implant*

Spectral analysis of the PD patient without dopaminergic medication showed an oscillatory pattern characterized by different rhythms: the spectral power in the low frequencies was lower than in the total beta band, both in the GPi and in the STN (Table I). Also, the bispectral analysis in the off dopaminergic condition showed that both the low frequencies and the low beta generated second harmonics [Fig. 2(b) and Fig. 3(b)]: a significant bicoherence peak was detected in ROI 1 (centered on [2.9 Hz, 2.9 Hz], in the GPi and on [3.9 Hz, 3.9 Hz] in the STN) and in ROI 2 (centered on [12.2 Hz, 12.2 Hz], in the GPi and on [14.1 Hz, 14.1 Hz], in the STN). In the STN, bicoherence had a significant peak also in ROI 3, centered on [16.6 Hz, 3.9 Hz].

After the administration of a clinical effective levodopa dose, the power spectrum displayed the expected changes: the low frequencies power increased, whereas the low-beta power decreased; the high beta power remained almost unchanged or slightly increased both in the GPi and in the STN (Table I). The

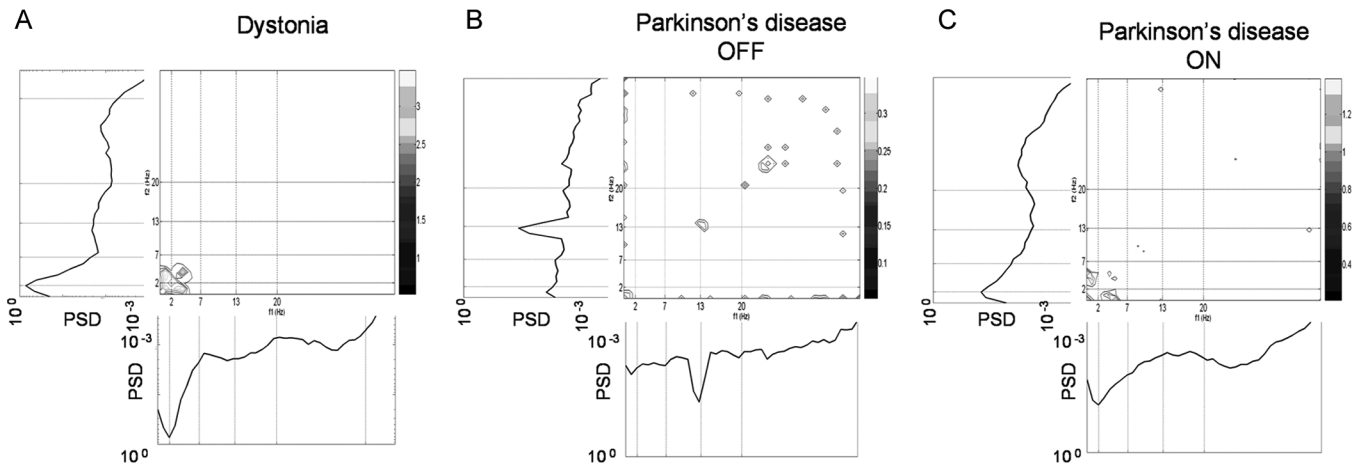


Fig. 3. Examples of significant bicoherence of the globus pallidus (GPi) local field potentials (LFPs) in dystonia (a) and Parkinson's disease (PD, Off levodopa condition: b; On levodopa condition: c). Only bicoherence values greater than the threshold for significance (see methods) are shown. Each panel is organized as in Fig. 2: the central 2-D plot shows the bicoherence of the GPi LPF signal as a function of frequencies $f_1$ ($x$-axis, in hertz ) and $f_2$ ($y$-axis, in hertz ). Level-lines in the plot represent bicoherence values grey-scale coded as indicated in the bar on the right. Power spectrum of the signal is presented in the left plot and in the lower plot in correspondence to the two frequency axes. Diagonal in the central plot defines the two regions of symmetry of the bispectral plane in the lower plot in correspondence to the two frequency axes. Diagonal in the central plot defines the two regions of symmetry of the bispectral plane.

pattern of nonlinear interactions, as shown by bispectral analysis, revealed a decrease in all the interactions between rhythms and a shift to a condition very similar to that of the dystonic patients [Fig. 2(c) and Fig. 3(c)]. In particular, there was a significant bicoherence peak only in ROI 1, centered on (4.8 Hz, 4.8 Hz) both in the GPi and in the STN [Fig. 3(c)]. Consistently, bispectral power increased in ROI 1 and decreased in ROI 2 and ROI 3 (Table I).

### C. Comparison With the Control Parkinsonian Group

Results of bispectral analysis in the patient affected by PD were compared with that obtained in a PD population. Table I shows the spectral and bispectral power in the off and in the on medication condition for the parkinsonian control group. The parkinsonian control population was significantly normal (i.e., nonnormality was rejected) in all the ROIs analyzed and in both the condition, thereby ensuring that the comparison procedures were consistent (off medication—$\mathrm{ROI}\ 1 : p = 0.16$;$\mathrm{ROI}\ 2 : p = 0.65$; $\mathrm{ROI}\ 3 : p = 0.32$; on medication—$\mathrm{ROI}\ 1 : p = 0.16$; $\mathrm{ROI}\ 2 : \mathrm{p} = 0.65$; $\mathrm{ROI}\ 3 : p = 0.32$).

When the PD patient was off medication, STN and GPi bispectral power in all ROIs were not different from those of the control population in the off medication (GPi—$\mathrm{ROI}\ 1 : |\mathrm{Z}| = 0.504$, $\mathrm{ROI}\ 2 : |\mathrm{Z}| = 0.687$, $\mathrm{ROI}\ 3 : |\mathrm{Z}| = 0.906$; STN—$\mathrm{ROI}\ 1 : |\mathrm{Z}| = 0.566$, $\mathrm{ROI}\ 2 : |\mathrm{Z}| = 0.486$, $\mathrm{ROI}\ 3 : |\mathrm{Z}| = 0.805$). Also, when the PD patient was on medication, STN and GPi bispectral power in all ROIs were not different from those of the control population in the on medication (GPi—$\mathrm{ROI}\ 1 : |\mathrm{Z}| = 0.525$, $\mathrm{ROI}\ 2 : |\mathrm{Z}| = 0.121$, $\mathrm{ROI}\ 3 : |\mathrm{Z}| = 0.744$; STN— $\mathrm{ROI}\ 1 : |\mathrm{Z}| = 0.566$, $\mathrm{ROI}\ 2 : |\mathrm{Z}| = 0.259$, $\mathrm{ROI}\ 3 : |\mathrm{Z}| = 0.744$).

As expected, the mean bispectrum was different in different ROIs (ANOVA, main factor ROI: $p < 0.000001$). More importantly, we found significant differences in individual ROIs across pathological conditions (ANOVA, interaction factor $\mathrm{ROI} \times \mathrm{condition} : p < 0.000001$). One-way ANOVA with post-hoc comparison in each ROI disclosed that in dystonic patients the mean bispectrum in ROI 2 was significantly lower compared to parkinsonian patients OFF levodopa ($p = 0.029$) but not significantly different from that of the parkinsonian patients ON levodopa ($p = 0.3$).

## IV. Discussion

Bispectral analysis disclosed that the rhythms expressed in the GPi of the untreated PD patient are similar to those observed in the STN and are characterized by nonlinear interactions. Conversely, in the dystonic GPi, as well as in the parkinsonian GPi after dopaminergic medication, the rhythms are substantially independent. These results were confirmed by the comparison between the present data and a larger sample of PD patients previously described [38]. In particular, this comparison disclosed that the GPi of dyskinetic patients is similar to the STN of the PD patients after receiving dopaminergic medication. The interactions between rhythms in the human GPi are therefore related to the patient's clinical condition. The interpretation of these interactions is likely critical for fully understanding the role of LFP rhythms in the pathophysiology of human basal ganglia.

The bispectrum has gained frequent application in clinical practice thanks to the introduction of the BIS index (BIS), a strong indicator for the intraoperative monitoring of the level of anesthesia. In addition to this role in clinical practice, results of bispectral analysis can be viewed within the framework of experimental data and can help clarifying the functional organization of the human central nervous system. For instance, the bispectrum helped in clarifying the origin of the burst-inter-burst pattern in healthy newborns sleep: the burst phase seems to be due to an amplitude modulation, generated by the nonlinear interaction between a slow wave and a faster wave [74].

From a signal processing point of view, the investigation of nonlinear interactions can help to correctly interpret the power spectrum. In the PD patient, the oscillatory pattern shown by the power spectrum contains also activity due to harmonics and, therefore, the functional definition of the LFP rhythms becomes difficult. The knowledge gained with the bispectrum permits,

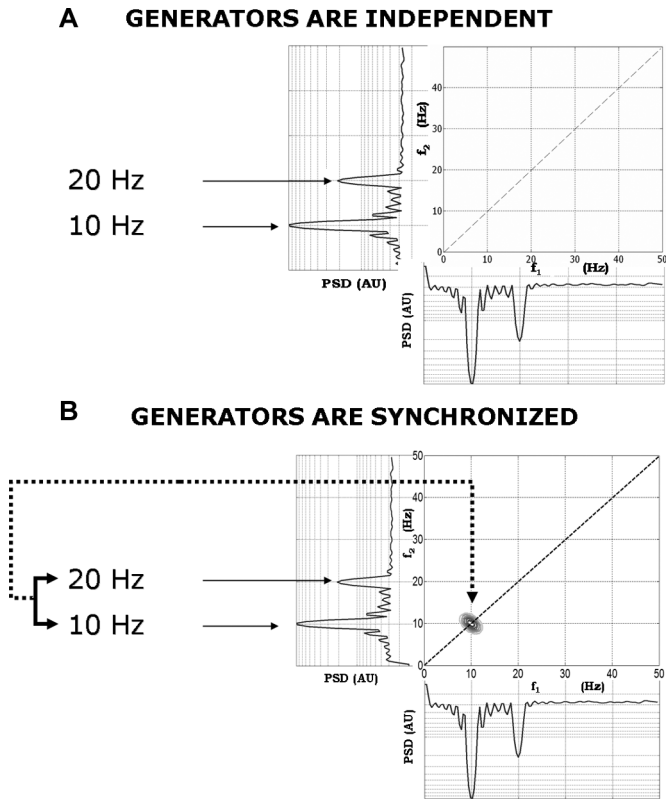


Fig. 4. Possible physiological meaning of nonlinear interactions detected by bispectral analysis. The two solid arrows represent simulated LFP oscillations (in this particular case one produces 10 Hz oscillation and the other one produces 20 Hz oscillation). Power spectrum and the bispectrum produced by the signal generated by the two oscillations are represented as in Fig. 2 in the right part of the two panels. When the two populations are independent (panel A), the rhythms generated are also independent. Rhythms are visible in the power spectrum. Bispectrum does not show any peak in correspondence to the oscillatory rhythms. Conversely, when a common input synchronizes the two populations, also the rhythms expressed are phase-coupled and, therefore, not independent (panel B). In this case, the bispectrum shows a peak at (10 Hz, 10 Hz), representing the nonlinear interaction between the 10 Hz and the 20 Hz rhythm. Details about the simulated LFPs can be found in [38].

if not a real quantification, at least a qualitative distinction between the independent activity of LFP rhythms and the synchronized activity due to the interaction between rhythms.

From a pathophysiological point of view, our results disclose that the altered synchronization pattern is shared between STN and GPi in the untreated PD, suggesting that the loss of synchronization at the STN level likely extends to the entire basal ganglia circuit and possibly also to the cortico-basal ganglia-thalamo-cortical loop. The results on the STN LFPs in the PD patient are in agreement with previous findings about the effect of levodopa administration on the interactions between rhythms in PD [38]. Coherence analysis had already revealed that the altered beta activity in the STN was reflected in the GPi and in the motor cortex [29], [44], [50], [61]. This coherence, projecting from the output structure of the basal ganglia back to the motor cortex and affecting the entire information processing loop, was suggested to lead to the altered motor behavior of PD [29], [44], [50], [61].

Conversely, in the GPi of the dystonic patients and of the PD patient after dopaminergic medication, the LFP pattern is characterized by a strong activity in the low-frequency band and by independence between rhythms. Our results are in agreement with previous studies on GPi LFPs, suggesting a similarity between the GPi oscillatory pattern in dystonia and treated PD [29], [41]. Indeed, hyperkinetic movements characterize the clinical picture of both dystonic patients and treated parkinsonian patients. The network low-frequency oscillation likely reflects, at the neuronal level, the abnormal burst-like pallidal firing pattern observed in dystonic patients [41], [75], [76]. Bispectral analysis showed that the low-frequency band (2–7 Hz) generates a second harmonic (4–14 Hz), mostly included in the low-frequency band itself: the activity in the low-frequency band is composed by a very slow oscillation and by its harmonics, resulting in the broadband peak observable in the power spectrum. As the same pattern is also displayed in the parkinsonian STN on medication, our result extend previous findings on the spectral coherence between STN and GPi in the low-frequency band in patients affected by hyperkinetic disorders [29]. The high synchronization of the oscillatory activity in the low-frequency range is associated with levodopa-induced dyskinesias [19]. We observed an high nonlinear interrelation within the low-frequency band, both in the STN and in the GPi, in dystonic and in PD patients in the on condition. The presence of multiple harmonics within the low-frequency rhythm in both the STN and the GPi could contribute to the increased low-frequency rhythm within the nuclei and, also, to the increased linear coherence between the nuclei observable in correspondence to hyperkineasis.

Despite the suggested role of interactions between rhythms detected by means of bispectral analysis, their origin is unclear. Nonlinear interactions could reflect the synchronization between two or more generators. LFPs generators are not single neurons, but populations of synchronized neurons. Therefore, the interaction between rhythms could be due to a common network input, able to synchronize the output of the neural networks generating LFPs (Fig. 4). However, it cannot be *a priori* excluded the possibility that the observed nonlinearity could be the result of a nonlinear behavior of a single oscillator.

In conclusion, bispectral analysis allowed us to quantify the degree of synchronization between different rhythms in human GPi and STN in different pathologies, providing new elements to extend the current pathophysiological model of the human basal ganglia.

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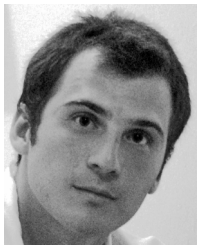

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