EJN European Journal of Neuroscience

FENS Federation of European Neuroscience Societies

*European Journal of Neuroscience, Vol. 42, pp. 2164–2171, 2015* doi:10.1111/ejn.12980

NEUROSYSTEMS

# Interaction of synchronized dynamics in cortex and basal ganglia in Parkinson's disease

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*Keywords*: EEG, LFP, subthalamic nucleus, synchronization

## Abstract

Parkinson's disease pathophysiology is marked by increased oscillatory and synchronous activity in the beta frequency band in cortical and basal ganglia circuits. This study explores the functional connections between synchronized dynamics of cortical areas and synchronized dynamics of subcortical areas in Parkinson's disease. We simultaneously recorded neuronal units (spikes) and local field potentials (LFP) from subthalamic nucleus (STN) and electroencephalograms (EEGs) from the scalp in parkinsonian patients, and analysed the correlation between the time courses of the spike–LFP synchronization and inter-electrode EEG synchronization. We found the (non-invasively obtained) time course of the synchrony strength between EEG electrodes and the (invasively obtained) time course of the synchrony between spiking units and LFP in STN to be weakly, but significantly, correlated with each other. This correlation is largest for the bilateral motor EEG synchronization, followed by bilateral frontal EEG synchronization. Our observations suggest that there may be multiple functional modes by which the cortical and basal ganglia circuits interact with each other in Parkinson's disease: not only may synchronization be observed between some areas in cortex and the basal ganglia, but also synchronization within cortex and within basal ganglia may be related, suggesting potentially a more global functional interaction. More coherent dynamics in one brain region may modulate or activate the dynamics of another brain region in a more powerful way, causing correlations between changes in synchrony strength in the two regions.

## Introduction

Excessively strong, weak or otherwise disorganized patterns of synchronous neural activity are believed to contribute to generation of symptoms in different neurological and psychiatric disorders including Parkinson's disease (Schnitzler & Gross, 2005; Uhlhaas & Singer, 2006). In particular, the low-dopamine state as seen in Parkinson's disease (PD) has been associated with increased power and synchrony of oscillatory activity in the beta frequency band (Hammond *et al.*, 2007; Eusebio & Brown, 2009; Stein & Bar-Gad, 2013; Brittain *et al.*, 2014).

This activity is widespread in cortical and basal ganglia (BG) circuits. The oscillations in the BG and in cortex frequently exhibit synchrony or other types of correlations, pointing to the existence of multiple functional cortical–subcortical loops (e.g., Goldberg *et al.*, 2004; Fogelson *et al.*, 2005; Sharott *et al.*, 2005a; Hirschmann *et al.*, 2011; Litvak *et al.*, 2011; Moran *et al.*, 2011; de Hemptinne *et al.*, 2013; Shimamoto *et al.*, 2013). The degree of cortical–subcortical synchrony is affected by dopaminergic status (e.g., Sharott *et al.*, 2005b; Mallet *et al.*, 2008; Hirschmann *et al.*, 2013). This interaction between BG and the cortex is expected given the direct and indirect anatomical connections between cortex and different BG nuclei. These observations suggest that cortex–BG coupling may be important for normal physiology of the BG and that its dysfunction may play a role in the PD symptomatology.

These functional connections between the cortex and BG are frequently studied by analysing the synchrony between signals recorded from the BG (either spiking units or local field potentials; LFPs) and signals from the cortex (see references above). This approach provides some measures of how neural activity (one neuron or many) at one location follows neural activity in another location. However, cortical circuits may affect BG circuits (and vice versa) in many different ways. Here we are interested in how the degree of synchrony within cortical areas is related to the degree of synchrony in the BG. In other words, not only can the dynamics of neurons in one place be related to the dynamics of neurons in another place (functional connection between dynamics of neurons), but the dynamics of synchrony in one brain area may be related to

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*Received 23 December 2014, revised 26 May 2015, accepted 5 June 2015*

the dynamics of synchrony in another brain area (functional connections between dynamics of brain areas, which ultimately, of course, are reliant on direct or indirect connections between neurons from these brain areas).

In this study, we considered the temporal dynamics and correlation of cortical synchronization and BG synchronization in the beta band in parkinsonian patients. We hypothesized that the strength of cortical synchrony and synchrony in BG are related. We explored this relationship and determined how it differs between different cortical areas. To study this, we simultaneously recorded neuronal units and LFP from subthalamic nucleus (STN) as well as scalp electroencephalograms (EEGs) in PD patients, and analysed the correlation between the dynamics of synchronous activity of spike–LFP and the dynamics of inter-electrode synchronous activity of EEGs. Thus we explored the functional connections between the dynamics of cortical areas and dynamics of subcortical areas in PD.

## Materials and methods

### *PD subjects and surgery*

The study was approved by Indiana University IRB and conforms with the Declaration of Helsinki. The study was undertaken with the understanding and written consent of each participating subject.

Ten patients with Parkinson's disease who underwent microelectrode-guided implantation of deep-brain stimulation (DBS) electrodes in the STN in Indiana University Hospital were included in the study (see Table 1 for detail). Seven of these patients were male and three were female, ages 64 ± 6.94 years, time between disease diagnosis and surgery was 9.90 ± 4.07 years, and the UPDRS score was 45.06 ± 8.64 off-medication and 19.50 ± 3.52 on-medication. These patients include all the patients in our movement disorders surgical program for whom bilateral EEG and depth recordings were available, who exhibited hypokinetic symptoms and exhibited no or only weak rest tremor, and who consented to participate in the study. The decision to perform the surgery was not influenced by subsequent inclusion of the data in the study. The surgical procedure was carried out using intravenous sedation with dexmedetomidine and local anesthesia. The procedures followed standard stereotactic surgical protocols. Our earlier study (Park *et al.*, 2010) describes this in more detail.

More specifically, patients were placed in a Leksell stereotactic frame. A contrasted volume-acquisition MRI scan was performed and transferred to a Stealth Station intraoperative navigation computer (Medtronic Navigation, Louisville, CO, USA). Target selection was performed indirectly with respect to anterior commissure (AC) and posterior commissure (PC). Preliminary targets in left and right STN, respectively, were selected with the following coordinates: $x$ = 12.00 mm left (right) of midline; $y$ = 2.0 mm behind mid-commisural point; $z$ = 4.0 mm below AC–PC plane. Coordinates could be modified slightly to accommodate individual variations in MRI-documented anatomy. An FHC Microdrive device (FHC, Bowdoin, ME, USA) was used to advance a microelectrode toward and past the previously selected preliminary target. The microelectrode was considered to be within STN when dense, somewhat irregular, high-amplitude action potentials were suddenly recorded after a period of relative silence as the microelectrode passed through the fields of Forel below the thalamus. The depths of recording locations (with respect to the planned target) were −0.66 ± 1.73 mm (left side) and −0.78 ± 1.54 mm (right side). Finally, the DBS electrode was implanted according to the data obtained by microelectrode targeting. The DBS electrode implantation location was confirmed by postoperative MRI. At the time of surgery, patients had been off antiparkinsonian medication for at least 12 h.

TABLE 1. Summary of patients' data

| Age (years) | Disease duration (years) | Gender | UPDRS | |
|---|---|---|---|---|
| | | | On L-DOPA | Off L-DOPA |
| 61 | 13 | M | 20 | 54 |
| 63 | 14 | M | 18 | 48 |
| 62 | 10 | M | * | * |
| 76 | 7 | M | 25 | 40 |
| 61 | 9 | F | * | 29 |
| 58 | 9 | M | 18 | 43 |
| 59 | 7 | F | 22.5 | 45 |
| 58 | 18 | M | 14 | 38.5 |
| 65 | 8 | M | 19 | 57 |
| 77 | 4 | F | * | 51 |

*Data not available.

### *Normal subjects*

We used publicly available EEG data from 109 neurologically healthy human subjects using the BCI2000 system (Schalk *et al.*, 2004; http://www.bci2000.org) and available at PhysioNet (Goldberger *et al.*, 2000; http://www.physionet.org).

### *Electrophysiological recordings in PD patients*

BG recordings were obtained with 80% platinum, 20% iridium glass-insulated microelectrodes (FHC), with impedance, measured in the brain at 1 kHz, being in the range 0.5–1.0 MΩ. The recordings were made with Guideline System 4000 (FHC), modified by adding LFP and EEG recording capabilities. The recording system amplified the depth electrode signal (5000×) and filtered it into two frequency bands: 300 Hz to 5 kHz and 0–200 Hz to obtain spiking neuronal units and LFP, respectively. Four scalp EEGs (Fp1, C3, Fp2, C4) were placed according to the 10 : 20 international system and referenced to linked ears. EEG signals were amplified (5000×) and filtered at the same frequency band as LFP. Spiking extracellular activity signal, LFP and scalp EEG were digitized at 20 kHz and saved for off-line analysis. All signals (extracellular spiking units, LFP and EEG) were examined off-line by visual inspection before frequency analysis was performed. Spikes were threshold-extracted and then spike sorting was performed to extract single-unit activity. The average duration of recorded episodes was 166 ± 35 s. An example of the data is shown in Fig. 1, with power spectral density and magnitude squared coherence in the subplots A and B, and the processed data obtained from the raw data in subplots C, D, F and G.

### *EEG recordings in normal subjects*

We used 64-channel EEG of the international 10–10 system at the sampling rate of 160 Hz recorded from 109 normal human subjects using the BCI2000 system and available at PhysioNet (see Normal subjects above). Recordings from the four electrodes positioned as in the Parkinsonian patients (Fp1, C3, Fp2, C4) were used. Each subject was recorded for 1 min at rest with eyes open. All signals were referenced to the mean EEG of two ears.

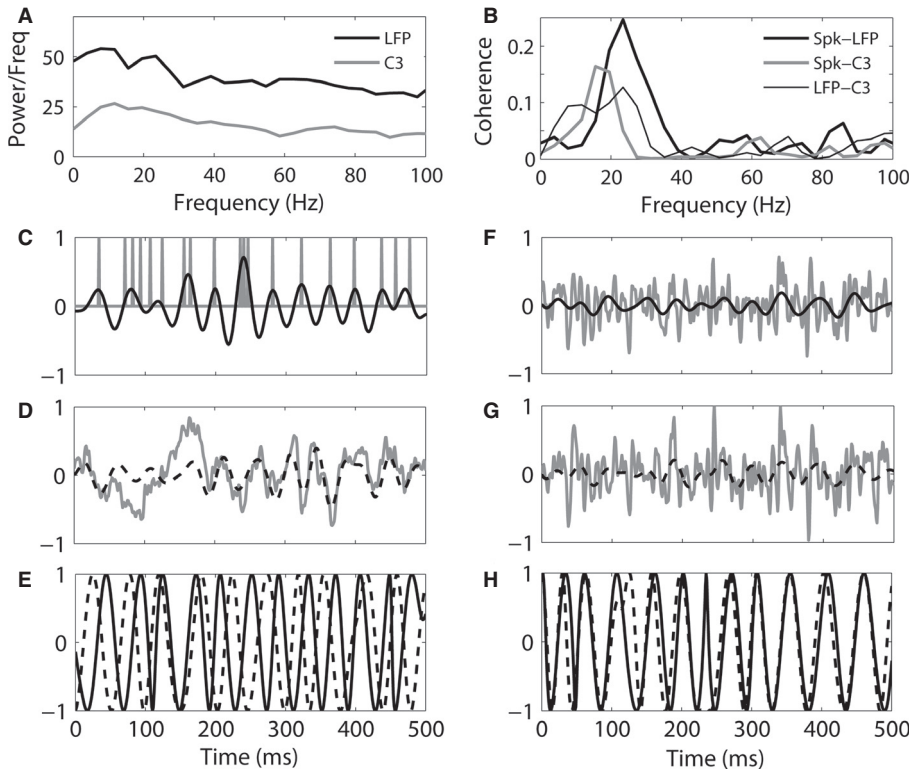


FIG. 1. (A) Examples of power spectral density for LFP (black line) and motor C3 (gray line) from a single PD patient and (B) the corresponding magnitude squared coherence for spiking-LFP (thick black line), spiking-C3 (thick gray line) and LFP–C3 (thin black line). Notch filters were used to remove main line effects around 60 Hz. Unfiltered and filtered signals with the sines of their phases from a single PD patient: (C) spiking unit, (D) LFP, (F) C3 EEG and (G) C4 EEG. Gray lines represent the unfiltered signals and black solid or dotted lines represent the signals filtered in the beta-band (10–30 Hz). Subplots (E) and (H) present the sines of the corresponding phases [sin($\phi$ ($t$))] of the filtered signals from (C and D) and (F and G) respectively. Relative arbitrary units are used in C, D, F and G (the computation of the phase-locking is insensitive to the amplitude).

### *Phase-locking analysis*

All signals were Kaiser-windowed and digitally filtered with a finite impulse response filter to extract beta band, defined here as 10–30 Hz, and gamma band, defined here as 35–90 Hz. For gamma band filtering, we used notch filters to remove main line effects around 60 Hz, and all parameters of temporal intervals used for computation were changed by a factor of three to have similar number of cycles of oscillations in the analysis of the beta and gamma bands. Zero-phase filtering was used to avoid phase distortions. Phase was extracted via Hilbert transform resulting in two signals, $\phi_1$ ($t$) and $\phi_2$ ($t$) (see Pikovsky *et al.*, 2001; Hurtado *et al.*, 2004). Examples of raw and filtered signals from a single unit (Spike), LFP, C3 and C4, and resulting phases in the beta band, are presented in Fig. 1. The following widely used measure of the strength of phase locking between these two signals was calculated:

$$\gamma = \left\| \frac{1}{N} \sum_{j=1}^{N} e^{i\theta(t_j)} \right\|^2,$$

where $\theta$ ($t_j$) = $\phi_1$ ($t_j$) − $\phi_2$ ($t_j$) is the phase difference, $t_j$ are the times of data points and $N$ is the number of all data points during the given time interval. The values of this phase-locking index vary from 0 (no phase locking) to 1 (perfect phase locking). This kind of phase synchrony index has been used to study neural oscillatory synchronization of widely varying strength (e.g., Lachaux *et al.*, 1999; Pikovsky *et al.*, 2001; Hurtado *et al.*, 2004).

We observed that all ten patients showed significant power spectrum peaks for LFP and motor EEGs in some time intervals in the beta frequency band by using signal to noise ratio (SNR) criterion defined as the peak value of the power spectrum in the beta band being at least twice as much as the average spectral power in the broader interval 6–55 Hz. The same situation was also observed for the case of coherence between the pairs of spiking and LFP and EEG–EEG signal pairs studied here with similarly defined SNR criterion for magnitude squared coherence.

### *Quantifying the interactions between synchronized dynamics in cortical and subcortical circuits*

We first computed the Pearson linear correlation between BG recordings (spiking neural unit or LFP) and cortical recordings (EEG) after these recordings were filtered in the beta and gamma frequency bands. At beta band, they were correlated over a time window of 10 s and with relative time lags varying up to 750 ms, then the maximal value of correlation was identified. There are eight different pairs of signals: Spike–Ipsilateral Frontal EEG, Spike–Ipsilateral Motor EEG, Spike–Contralateral Frontal EEG, Spike–Contralateral Motor EEG, LFP–Ipsilateral Frontal EEG, LFP–Ipsilateral Motor EEG, LFP–Contralateral Frontal EEG and LFP–Contralateral Motor EEG (here Motor and Frontal refer to C3/C4 and Fp1/Fp2 electrodes respectively; Ipsilateral and Contralateral refer to the position of the EEG electrode with respect to the depth recording position). These pairs of signals were correlated and the resulting

correlation coefficients represent the correlation between beta or gamma band cortical activity in an area beneath an EEG electrode and BG beta or gamma band activity in the area around a microelectrode.

In order to assess the relationship between synchronized oscillatory activities in the cortical circuits (EEG synchronization) and in the BG (Spike and LFP synchronization), we performed an analysis inspired by ideas presented in Hurtado *et al.* (2004). In the beta band, we computed the phase-locking index, $\gamma$, over sliding time-windows of 1 s duration shifted by 5 ms for different pairs of signals. In the gamma band, we divided 1 s time-windows into three intervals and computed the phase-locking index, then took the mean value of these phase-locking indices. The resulting time-series of $\gamma(t)$ was smoothed with a third-order Savitzky–Golay filter (Orfanidis, 1996). Smoothing the curves with this filter removes fast but small fluctuations and allows us to focus on more stable and slow variations of synchrony in time. Figure 2 illustrates this temporal dependence of synchrony between spiking neural units and LFP and between two EEG electrode signals [$\gamma_{(Spike,LFP)}(t)$ and $\gamma_{(C3,\ C4)}(t)$] for a single subject before and after the smoothing in the beta band. The smoothing length was set to 305 ms (it is 305 ms, not 300 ms, because the filtering procedure requires it to be an odd multiple of the 5 ms shift, but the results are not substantially altered if this value is changed by this amount) so that small fluctuations are removed, but fluctuations on the scale of 1 s (which is similar to the duration of the window used to compute $\gamma$) are preserved.

To determine the correlation between $\gamma_{(Spike,LFP)}(t)$ and $\gamma_{(EEG1,\ EEG2)}(t)$, we computed the Pearson linear correlation between smoothed $\gamma(t)$ for these two time series for a 10 s window with varying time-lags between the time-series of up to 750 ms. Then the maximal correlation coefficient value was selected. These linear correlations [computed over smoothed $\gamma(t)$] describe how the synchrony in cortex and synchrony in BG are correlated on relatively slow time-scales (much longer than one cycle of oscillations). Note that there are six possible combinations of EEGs. We will call them Bilateral Frontal, Bilateral Motor, Ipsilateral Frontal–Ipsilateral Motor, Ipsilateral Frontal–Contralateral Motor, Contralateral Frontal–Ipsilateral Motor, and Contralateral Frontal–Contralateral Motor. We computed the correlation between $\gamma_{(Spike,LFP)}(t)$ and $\gamma_{(EEG1,\ EEG2)}(t)$ at each recording side (left and right) for each patient.

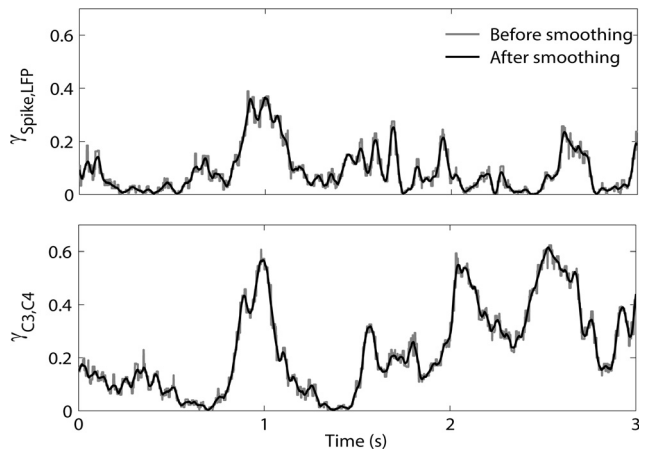


FIG. 2. The time courses of (A) $\gamma_{(Spike,LFP)}(t)$ and (B) $\gamma_{(C3,C4)}(t)$ from a parkinsonian patient before (gray) and after (black) smoothing in the beta band (10–30 Hz). Note that the value of $\gamma(t)$ at each instant of time is not an 'instantaneous synchrony strength' (instantaneous synchrony does not exist), but a value of phase-locking index $\gamma$ computed over the window of pre-set duration, which includes sufficiently many cycles of oscillations.

### Statistics

Data analysis was performed in MATLAB (Mathworks, Natick, MA, USA) and R (www.r-project.org). Unless specified otherwise, all comparisons were first subjected to ANOVA testing. The detail statistical methods are as follows.

To determine the statistical significance of the correlations, we generated surrogate correlation values data by computing correlations for pairs of signals of the relevant type [neural unit/LFP and EEG; $\gamma_{(Spike,LFP)}(t)$ and $\gamma_{(EEG1,\ EEG2)}(t)$] chosen randomly and independently from the set of all patients (excluding combinations from the same subject at the same time). To match the sample size, all surrogate data were selected at each iteration whenever we computed the correlation value for each patient. The surrogate data provides the situation in which the signal pairs should not be correlated just by construction. Thus it allows estimation of the significance of the observed correlation values.

When we compared healthy and parkinsonian EEG data (Fig. 3) we compared the distributions of synchrony index $\gamma$ for different EEG pair combinations. We performed ANOVA with two factors: group (normal subjects and PD patients) and EEG pairs (six pairs) followed by paired *t*-test comparisons. To study correlations between cortical and subcortical activity we compared the distributions of Pearson's linear correlation coefficients between filtered BG recording (spikes or LFP) and filtered EEGs (Fig. 4). We first performed ANOVA with two factors: depth recordings (spikes and LFP) and EEGs (four EEGs). Then we checked the significance of correlation values using surrogate data. Finally, when we studied correlations between synchrony in cortical and subcortical areas we compared the distributions of Pearson's linear correlation coefficients between synchrony index $\gamma_{(Spike,LFP)}(t)$ and $\gamma_{(EEG1,\ EEG2)}(t)$ (Fig. 5). We first performed one-way ANOVA with a factor: pairs of $\gamma_{(Spike,LFP)}(t)$ and $\gamma_{(EEG1,\ EEG2)}(t)$. Further analysis was performed with Tukey's *post hoc* test or paired *t*-test at the significance level of $\alpha = 0.05$ or $\alpha$ appropriately adjusted for the Bonferroni correlation (see Results). To check the significance of correlation values we again used the surrogate data.

## Results

### The strength of synchrony between EEG electrode pairs in normal subjects and PD patients

BG spiking units and LFP signals cannot be obtained from the normal subjects for obvious ethical reasons. Thus to put the study in

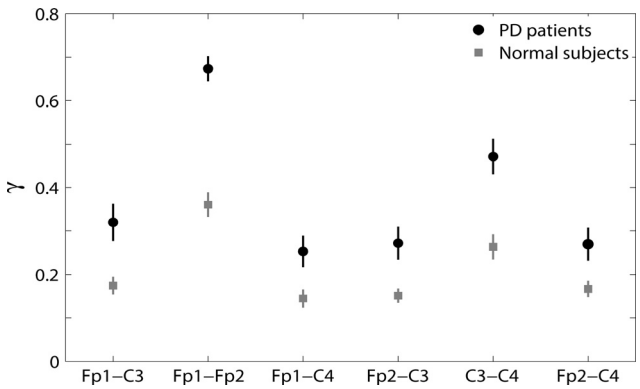


FIG. 3. The synchrony index $\gamma$ for different EEG pairs for normal subjects (gray squares) and PD patients (black circles) in the beta band (10–30 Hz). Mean $\pm$ SEM of $\gamma$ is plotted.

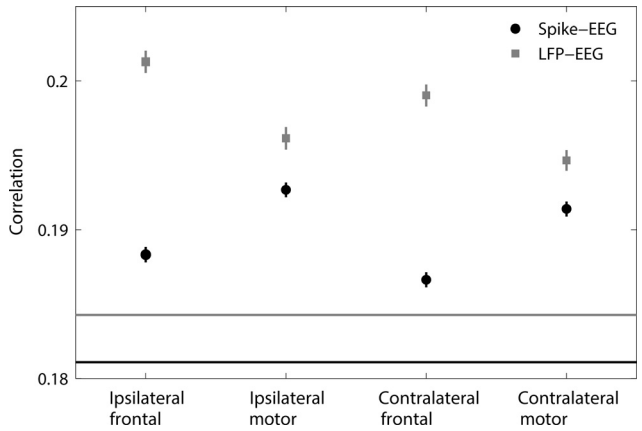


FIG. 4. Pearson linear correlation coefficient between LFP and EEG (gray squares) and spiking unit signal and EEG (black circles) in the beta band (10–30 Hz). Significance levels (horizontal gray and black lines) were computed with surrogate data. 'Ipsilateral' includes the cases where depth recording (either spiking unit or LFP) and EEG recording are on the same side of the brain (EEG recordings ipsilateral to the depth electrode). 'Contralateral' includes the cases where they are on the opposite sides (EEG electrodes contralateral to the depth electrode). 'Frontal' represents Fp1/Fp2 in EEG electrodes. 'Motor' represents C3/C4 EEG electrodes. Mean ± SEM of the correlation coefficients is plotted.

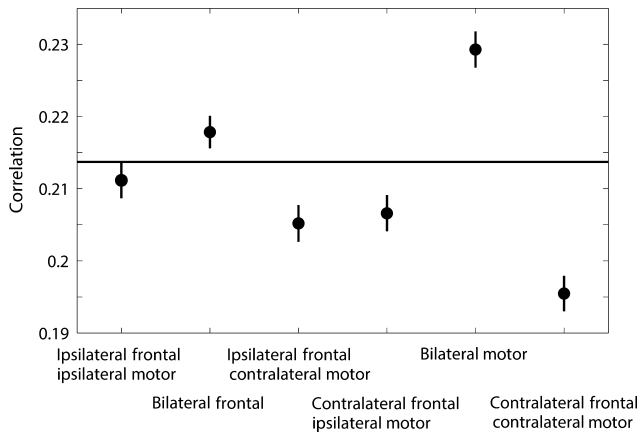


FIG. 5. Pearson linear correlation coefficient between $\gamma_{(Spike,LFP)}(t)$ and $\gamma_{(EEG1,EEG2)}(t)$ from parkinsonian patients in the beta band (10–30 Hz). The significance is estimated with the surrogate data (horizontal black line). Mean ± SEM of the correlation coefficients was plotted.

the context of the healthy brain dynamics (as well as in the context of earlier studies of synchronization in Parkinson's disease) we compared the synchrony between EEG recordings in normal subjects and parkinsonian patients. More specifically, we compared the average phase-locking strength $\gamma$ for different pairs of EEG signals in patients and normal subjects (we randomly chose normal subjects to match the sample sizes with PD patients).

The results of this comparison are presented in Fig. 3. To compare the distributions of $\gamma$ from normal subjects and PD patients across six different pairs of EEG electrodes, we first employed two-factor ANOVA (factors: groups and EEG pairs). In the beta frequency band, there were significant main effects of groups ($F_{1,228} = 85.30$, $P < 2 \times 10^{-16}$) and EEG pairs ($F_{5,228} = 32.44$, $P < 2 \times 10^{-16}$). There was also an effect of interaction between groups and EEG pairs ($F_{5,228} = 3.40$, $P = 0.00559$). The difference of $\gamma_{EEG1,\ EEG2}$ between PD patients and normal subjects was studied with a two-sided paired *t*-test at the significance level of $\alpha = 0.00833$ for the Bonferroni correction. There were significant differences in $\gamma_{EEG1,EEG2}$ between PD patients and normal subjects for Fp1-C3 ($t_{38} = 3.07$, $P = 0.0039$), Fp1-Fp2 ($t_{38} = 7.75$, $P = 2.45 \times 10^{-9}$), Fp2-C3 ($t_{38} = 2.92$, $P = 0.00591$) and C3-C4 ($t_{38} = 4.14$, $P = 0.000188$). There was no difference between PD patients and normal subjects for Fp1-C4 and Fp2-C4 at the significance level of $\alpha = 0.00833$. The overall levels of synchrony (see Fig. 3) for PD patients were significantly higher than those of normal subjects (Tukey's HSD, $P < 2.2 \times 10^{-16}$; Fig. 3).

### *Correlations between cortical (EEG) and subcortical (units and LFP) oscillatory activity*

In this section we consider how the activity in the BG is correlated with the activity in the cortex. We computed the Pearson linear correlation between filtered spiking unit signal and filtered EEGs or filtered LFP and filtered EEGs in the beta band (see Materials and Methods). These results are illustrated in Fig. 4. To compare the distributions of the correlations for spike–EEGs and LFP–EEGs across four EEG electrodes, we first employed two-factor ANOVA [factors: depth recordings (spiking unit and LFP) and four EEGs]. In the beta frequency band there were significant main effects of depth recordings ($F_{1,47816} = 324.29$, $P < 2.2 \times 10^{-16}$) and EEGs ($F_{3,47816} = 4.92$, $P = 0.00204$). There was also a significant effect of interaction between depth recordings and EEGs ($F_{3,47816} = 36.51$, $P < 2 \times 10^{-16}$).

To test the significance of the correlation values for spike–EEG and LFP–EEG, we compared these values with the surrogate data (pooled data) with the one-sided paired *t*-test with a significance level of $\alpha = 0.00625$ (see Materials and Methods). The correlation values of spike–EEG and LFP–EEG were greater than those obtained from the surrogates (Fig. 4). Next we employed one-way ANOVA (factor: four EEG pairs) to compare the distributions of the correlations for each spike–EEG and LFP–EEG. For both spike–EEG and LFP–EEG, there were significant effects of EEG pairs ($F_{3,23908} = 30.07$, $P < 2 \times 10^{-16}$ for spike–EEG; $F_{3,23908} = 16.27$, $P = 1.47 \times 10^{-10}$ for LFP–EEG). *Post hoc* testing indicated that spike–motor EEGs and LFP–motor EEGs were significantly different from spike–frontal EEGs and LFP–frontal EEGs (Tukey's HSD, $P \leq 0.000105$ for spike–EEGs; $P \leq 0.0282$ for LFP–EEGs). Note that the phase-locking index values for spike–EEG and LFP–EEG signal pairs for different EEG electrodes were very low. They were statistically significantly different from those obtained from surrogate data, but this statistical significance may not necessarily have many functional implications because of very low values observed.

In the gamma frequency band (35–90 Hz), we also employed two-factor ANOVA [factors: depth recordings (spiking unit and LFP) and four EEGs]. There was a significant main effect of depth recordings ($F_{3,11288} = 84.86$, $P < 2 \times 10^{-16}$) but no effect of EEGs ($F_{3,11288} = 1.55$, $P > 0.05$). Similar to the beta frequency band, the correlation values of spike–EEG and LFP–EEG were above those obtained from the surrogates.

Although the correlation values for different EEG electrode combinations were statistically significantly different, these differences were small (see Fig. 4). Nevertheless, these results indicated that there may be some correlation between oscillatory activities in BG and the cortex (which is, of course, not surprising and has been observed earlier with different measurements). We next explored the relation between the synchrony of activity within cortex and that within BG.

### *Correlations between dynamics of synchrony in cortical and BG areas*

In order to evaluate how the dynamics of synchrony in cortical and subcortical areas are related we first computed the time-dependent phase-locking strength index, $\gamma$, as described in Materials and Methods (see also Fig. 2). We then computed the Pearson linear correlation coefficient between $\gamma_{(Spike,LFP)}(t)$ and $\gamma_{(EEG1,EEG2)}(t)$ in PD patients. Indices *EEG*1, *EEG*2 were used to denote six EEG combinations we need to consider: Bilateral Frontal, Bilateral Motor, Ipsilateral Frontal–Ipsilateral Motor, Ipsilateral Frontal–Contralateral Motor, Contralateral Frontal–Ipsilateral Motor, and Contralateral Frontal–Contralateral Motor (note that we recorded spiking unit and LFP signals on both left and right sides, but not at the same time, simultaneously with four EEGs; see Materials and Methods). To estimate the significance of the correlation between $\gamma_{(Spike,LFP)}(t)$ and $\gamma_{(EEG1,EEG2)}(t)$, we used the correlation values from all the data pooled together (the data from different subjects) to obtain surrogate data (see Materials and Methods). These results are presented in Fig. 5.

To compare the distributions of the correlations among all six pairs, we first employed one-way ANOVA with EEG pairs as factor. In the beta frequency band there was a significant main effect of EEG pairs ($F_{5,28686} = 17.92$, $P < 2 \times 10^{-16}$). We further performed *post hoc* tests to find the differences between EEG pairs. Bilateral Motor was significantly different from all other pairs (Tukey's HSD, $P \leq 0.0323$). Similarly, Bilateral Frontal was significantly different from all other pairs (Tukey's HSD, $P \leq 0.0417$) except Ipsilateral Frontal–Ipsilateral Motor (Tukey's HSD, $P > 0.05$). To test the significance of the correlation values, we compared these values with the surrogates (pooled data), using one-sided paired *t*-tests with a significance level of $\alpha = 0.00833$. Only Bilateral Frontal ($t_{9562} = 3.24$, $P = 0.000605$) and Bilateral Motor ($t_{9562} = 6.01$, $P = 9.45 \times 10^{-10}$) had significantly higher correlation values than those of the surrogate.

Moreover, Bilateral Motor showed a significantly higher correlation value than all other pairs including Bilateral Frontal. This points to the way in which the dynamics of synchrony in cortical circuits and synchrony in BG are correlated over time for different cortical areas. The time course of bilateral synchronization of EEG over motor cortex is most strongly correlated with the time course of spiking unit–LFP synchronization in the STN. The time course of bilateral synchronization of EEG over frontal areas is also correlated with the time course of synchronization in the BG but to a lesser degree, while the time course of EEG synchronization for unilateral (whether ipsilateral or contralateral to the location of the depth recording) and bilateral motor–frontal pairs are not significantly correlated with the time course of synchrony in the BG.

In the gamma frequency band there was no main effect of EEG pairs ($F_{5,28686} = 0.89$, $P > 0.05$). Moreover, none of the EEG pairs was significantly higher than that of the surrogate (one-sided paired *t*-test, $t_{9562} < 2.38$, $P > 0.00833$) at the significance level of $\alpha = 0.00833$. Thus the correlations between dynamics of synchronization in cortical and in subcortical circuits in PD is frequency-specific and is significant for the beta band and nonsignificant for the gamma band.

## Discussion

### *Correlations between dynamics of synchrony strength in EEG signals and BG signals*

This study analysed correlations and synchrony in the beta and gamma bands in scalp EEG recordings and in recordings of spiking neural units and LFPs in the STN of parkinsonian patients.

We first compared the synchrony between EEG electrodes in parkinsonian and neurologically healthy humans. The recordings in normal subjects are not from a perfect control group. Normal subjects were not age-matched to the parkinsonian patients. EEG recordings in normal and parkinsonian subjects were performed in different settings (parkinsonian patients had their EEG recorded during a very special environment of stereotactic functional neurosurgery so there may be potential effects of drugs on EEG; furthermore, the recording equipment differed from that used in healthy subjects). We thus used the normal EEG data here only to put the parkinsonian data in the appropriate context. We observed that the synchrony between EEG electrodes in parkinsonian patients was higher than in healthy subjects (which fits the general paradigm of the elevated beta-band synchrony and hypokinetic symptoms in PD; see references in Introduction).

We found that the beta-band activity in STN of the BG (measured as activity in both the neural units and in LFPs) was weakly correlated with the cortical activity measured by EEG. Again, this is consistent with the 'beta synchrony' paradigm and with earlier results on the functional interactions between cortical and BG circuits (e.g., Fogelson *et al.*, 2005; Sharott *et al.*, 2005b; Hirschmann *et al.*, 2011; Litvak *et al.*, 2011; Shimamoto *et al.*, 2013).

This study also analysed the correlations between the time course of EEG–EEG synchrony and STN spiking unit–STN LFP synchrony. To do so we performed simultaneous intraoperative recordings of scalp EEG, STN spiking units and STN LFP in parkinsonian patients. To the best of our knowledge, this is the first time that simultaneous recordings of scalp EEG, STN spiking units and STN LFP have been performed in parkinsonian human subjects, and the first time that analysis of correlations between temporal dynamics of synchronies in different brain regions has been performed. The time course of the synchrony strength between EEG electrodes and the time course of the synchrony between spiking unit and LFP in STN were found to be weakly, but significantly, correlated. This correlation was found to be largest for the case of bilateral motor EEG (C3/C4). It was followed by bilateral frontal EEG (Fp1/Fp2) and unilateral motor–frontal (C3/Fp1 and C4/Fp2) electrode pairs. It was nonsignificant for contralateral, ipsilateral motor–contralateral frontal, and ipsilateral frontal–contralateral motor EEG electrode pairs.

The strength of synchrony between EEG electrodes (especially Fp1/Fp2 synchrony) may be affected by the relatively close position of the electrodes in space, so that they pick up parts of some common signal. However, what is being studied here is not the value of this synchrony but rather how its changes over time are correlated with the time-linked changes in the BG synchrony, so that the impact of cross-talk between the electrodes should not be substantial.

### *Correlation between dynamics of different brain regions*

As was discussed above, the functional coupling between oscillatory dynamics in cortex and BG was usually measured via synchrony between neural activity in the BG and neural activity in the cortex. Roughly speaking this kind of synchrony indicates that whenever electrical activity in cortical areas increases, electrical activity in the BG circuits increases too (maybe with some time lag, positive or negative, if this is not a zero-lag synchrony). This is synchronization between oscillatory activities in different brain regions.

However, not only can oscillations from different brain regions be functionally coupled, but whole brain regions may interact in a more global way. The dynamics of cortical and BG areas are accessed here via synchrony within each of the regions. In the cortex this is

synchrony between different EEG electrodes; in the BG this is synchrony between STN spikes and STN LFP (which may reflect input–output synchrony for STN, which gets substantial synaptic input from the external segment of globus pallidus; see discussion in Park *et al.*, 2010). The levels of synchrony in both brain regions fluctuate in time (e.g., EEG synchrony fluctuations (Ahn & Rubchinsky, 2013) and spike–LFP synchrony fluctuations (Park *et al.*, 2010; Rubchinsky *et al.*, 2012)). Using methods discussed above, the strength of the synchrony may be estimated over relatively short time intervals, allowing determination of the time course of synchrony.

One needs to interpret this time-dependent synchrony with care (Hurtado *et al.*, 2004). Two oscillations cannot be synchronous at an instant of time but they can be synchronous over a relatively short time interval, so that as we move the corresponding temporal analysis window in time we obtain the time course of synchrony fluctuations. Our observation of the correlations between time courses of synchrony in cortical and BG areas suggests that these brain regions interact so that temporal changes in the synchrony strength in one region implies changes in the synchrony strength in the other region. The methods used in the analysis consider time scales of hundreds of milliseconds and longer. This is necessitated first by the consideration of the beta band (~50 ms cycle of oscillations) and also the need to have tens of cycles of oscillations to obtain reliable estimates of synchrony. Thus the correlations of synchrony time courses shown in the current study imply that relatively slow (≥~1 s) changes in the dynamics of cortical circuits and dynamics of the BG are related.

### *Functional implications of interactions of synchronized dynamics in different brain regions*

The correlations between different brain regions suggest that there may be multiple functional modes by which the cortical circuits and BG interact with each other. The changes in synchrony in the brain regions, as they evolve in time over hundreds of milliseconds and longer, may suggest that the changes in the overall activation of the cortical and BG circuits are related. This picture suggests the following hypothetical possibility for cortex–BG interactions.

Temporal changes in synchrony strength in cortical or BG areas describe how the activity in these areas becomes more or less coherent in time. More coherent activity in one brain region is more likely to exert a more powerful impact on another brain region with which it interacts. This may or may not lead to an increase in synchrony between elements of different circuits. However, more coherent dynamics in one brain region may modulate or activate the dynamics of another brain region in a more powerful way, causing correlations between changes in synchrony strength in the two regions. Our correlative studies do not reveal the directionality of the interactions. However, given the multiple monosynaptic and polysynaptic connections between cortex and the BG as well as the fact that they all belong to a common cortex–BG–thalamus loop, the interaction between cortical circuits and BG may be mutual and bidirectional. The complex nature of cortex–BG interactions (synchrony between oscillations in different brain regions, slow correlations between synchronies within different brain regions) may suggest that the beta-band rhythmicity is involved in parkinsonian physiology on many temporal and spatial levels, and interactions facilitated by this beta-band activity are exhibited not only in the beta band but also on slower time scales (manifested by relatively slow changes in the beta-band synchrony strength).

The spatial organization of the correlation of variations in synchrony strengths has a specific structure: there are significant correlations of BG synchrony with bilateral EEG synchrony, mostly between motor areas but also between frontal areas, whereas unilateral correlations are not significant. Direct beta-band synchronization between the left and right hemispheres of the BG has been observed previously (de Solages *et al.*, 2010; Little *et al.*, 2013). However, our observations of cortical and BG synchrony interactions suggest the importance of interhemispheric interactions for the effects of coherence in cortical and BG areas on each other. The depth recordings were obtained from the parts of STN which are primarily motor circuits. However, frontal areas are also involved in the interaction between motor circuits of cortex and BG in the form of frontal interhemispheric coherence. These observations complement earlier observations of the frontal circuits' impact on motor parts of BG (e.g., Oswal *et al.*, 2013).

It may be interesting to consider different mechanisms of pathological beta band rhythmicities in light of the results of the present study. Whether they are cortex- or BG-related (or mediated by the striatum; McCarthy *et al.*, 2011), they are quite likely to be modulated by the interactions between these various regions of the brain.

The functional significance of cortical activation in PD has been studied with fMRI. It exhibits nontrivial spatial organization and differences from the normal subjects (e.g., Yu *et al.*, 2007; Tessa *et al.*, 2010). The cortical activation as measured by MRI may be related to the changes in coherence in cortical areas considered here, suggesting potential functional significance of synchrony variations in cortical and BG areas.

Finally, it is interesting to note that the observed correlations between dynamics of different brain regions is a relationship between invasively and non-invasively obtained measures. The time course of synchrony in cortical circuits is obtained from noninvasive EEG recordings, while the time course of synchrony strength in BG can be obtained only via depth electrodes. While the correlation between them is not very strong, it is nevertheless significant. Thus we can extract some knowledge about synchronous dynamics in subcortical areas from EEG measurements (in particular, from bilateral motor EEG synchrony). This may also be interesting, because these measurements can be performed in healthy individuals. If correlations of cortical and BG synchrony strength in healthy and parkinsonian individuals are similar, dynamics of BG synchrony in healthy subjects could be partially characterized by noninvasive measurements.

## Acknowledgements

This study was supported by IU-CRG.

## Abbreviations

BG, basal ganglia; DBS, deep-brain stimulation; EEG, electroencephalogram; LFP, local field potential; PD, Parkinson's disease; STN, subthalamic nucleus.

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