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The influence of Parkinson's disease on the functional connectivity of the motor loop of human basal ganglia

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ABSTRACT

Current basal ganglia models integrate information obtained from humans and animals to explain motor disorders in Parkinson's disease. These models explain some motor disturbances of Parkinson's disease (PD), but different clinical observations which remain unexplained have promoted the development of new basal ganglia (BG) models. The present study uses the time-relationship (partial correlation) of the BOLD-signal fluctuations to study the influence of PD on BG interactions of 17 age-matched controls (58.7 ± 5.3 years of age) and 24 PD patients (56.7 ± 8.4 years of age). Controls showed a complex functional connectivity of BG with a positive correlation between some nuclei (synchrony) and a negative correlation between other nuclei (anti-synchrony). This functional connectivity was different in PD-patients who showed: 1. an increased synchrony between the primary motor cortex(M1)-external pallidum(GPe), putamen(Put)-GPe, Put-subthalamic nucleus (STN), STN-internal pallidum (GPi), STN-motor thalamus (Tal), STN-GPi substantia nigra (SN) and SN-Tal, 2. a decreased synchrony between Put-GPi, GPe-STN, GPe-SN, STN-SN and GPi-SN, and 3. an increased anti-synchrony between GPe-SN and GPi-Tal. In control subjects, the motor-task increased the Put-Tal, GPi-SN and STN-Tal synchrony, decreased the STN-GPi and STN-SN synchrony and decreased the M1-GPe and the GPe-GPi anti-synchrony. The effect of the motor-task was very different in PD-patients, in whom it induced a decrease of the M1-GPe, STN-GPi and SN-Tal synchrony and a decrease of the GPe-Tal and GPe-SN anti-synchrony. Functional connectivity imaging methods may provide data that cannot be obtained by other methods in humans, and that may help to understand the physiology of BG and its deterioration in PD.

1. Introduction

Basal ganglia (BG) are composed of interconnected subcortical centers arranged in closed-loop circuits with the brain cortex. Current models include five parallel cortico-BG closed-loops, one of which is the basal ganglia motor circuit(**BGmC**). This circuit is composed of neurons projecting from the primary motor cortex(**M1**) to the putamen(**Put**), and from this center to the external globus pallidum(**GPe**), subthalamic nucleus(**STN**), internal globus pallidum(**GPi**) and substantia nigra reticulata(**SNr**). Motor information processed by these centers goes to the anterior thalamus (motor thalamus;**Tal**) and then returns to M1. Three main pathways have been described in the BGmC: the direct pathway (M1→Put→SNr/GPi→Tal→M1), the indirect pathway (M1→Put→GPe→STN→GPi/SNr→Tal→M1), and the hyperdirect pathway (M1→STN→SNr/GPi→Tal→M1) (esupp File 1-top), assuming that the overall dynamic of BGmC is dependent on the excitatory/inhibitory actions between the successive centers of these cortico-BG loops [1–3].

The **classical BG-model** has been widely used to justify motor disorders in Parkinson's disease (**PD**) (esupp File 1-bottom). These disorders are often considered as the consequence of a preponderance of the indirect pathway over the direct pathway, an imbalance induced by the degeneration of dopaminergic nigrostriatal neurons. However, this model cannot explain some key circumstances of the illness [4–7], a mismatch that could be associated to the fact that the model was initially developed from experimental data obtained in animals. Thus, there is growing interest in studying the human BG directly, an objective that can now be addressed with neuroimaging methods. The temporal relationship of the spontaneous BOLD-fluctuations of BG (functional connectivity MRI;**fcMRI**) [8] was used here to study the functional interaction of the BGmC centers in PD patients and control subjects. The partial correlation was used to prevent the spurious interactions associated to the global dynamic of the BG loops [9,10]. The

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grouping of BOLD-data for the creation of experimental groups was performed using regions of interest (ROIs) which represent the activity of individual BG. ROIs were carefully positioned in each center of each subject, thus avoiding inter-individual differences for the spatial location of the smallest BG from altering the assembly of the individual's data in the experimental groups [11,12]. Finally, the possible effect of the BG activity on the functional connectivity of these centers was tested by comparing data recorded during resting and motor activity.

2. Methods

2.1. Participants

Forty three right-handed volunteers participated in this study, 17 age-matched control subjects (8 males/9 females) with 56.7 ± 5.3 years of age (34–68 years), and 26 PD-patients (13 males/13 females) with 59.7 ± 8.4 years of age (40–73 years). Patients were diagnosed by two experienced neurologists and the severity of clinical motor symptoms was assessed according to the Hoehn & Yahr scale (1.70 ± 0.17) and Unified Parkinson's Disease Rating Scale III (12.23 ± 1.57). Only PD patients with an early-to-mid clinical motor stage (Hoehn/Yahr:I-II stage) were included in the study, and patients with a tremor-predominant symptomatology or an asymmetric right-left expression of motor disorders were excluded. Patients with dementia, brain abnormalities or any parkinsonism generated by other degenerative diseases were also excluded. Anti-parkinsonian drugs were withdrawn 24 h prior to the study. Control subjects had no history of brain injury, or neurological or psychiatric disorders. Written informed consent was provided by all participants, all procedures were in accordance with the ethical standard of the 1964 Helsinki declaration, and the study was approved by an institutional review board (Human Studies Committee-La Laguna University).

2.2. Data collection

The basic experimental procedures were similar to those previously reported [11,13]. Briefly, the BOLD-fluctuation of BG was used to study the functional connectivity of these centers in subjects who performed a motor-task or remained at rest. A block-task paradigm with interleaved "resting"/"motion" intervals was used [8,14]. During the motor-task block, subjects performed a repetitive sequence of finger extensions/flexions with the right-hand (from the little finger to the thumb and back to the little finger) that was monitored by a video camera. During the resting-task block, subjects did not perform any planned task. The transitions between the motor-resting and motor-task blocks were orally announced by a single word, "MOVE" to start motion and "STOP" to finish motion.

BOLD-contrast images (64x64 sampling matrix with voxels of 4x4x4 mm) were acquired (GE; 3.0 T) in a coronal plane (250 × 250 mm field of view) with gradient-echo (echo-planar imaging; repetition-time 1600 ms; echo-time 21.6msec; flip-angle 90°). 100 vol were recorded in each of the following task-blocks: motor block→resting block→motor block→resting block (400 vol = 100 vol x 2 motor-blocks x 2 resting-blocks). Frames 1–5 and 95–100 of each block were removed [15]. fMRI data were co-registered with 3D anatomical images (repetition-time 7.6 ms; echo-time 1.6 ms; flip-angle 12°; 250 × 250 mm field of view; 256x256 sampling matrix; voxels of 1x1x1 mm). The brain position of the smallest BG centers (e.g. STN) shows an inter-subject variability which hampers the precise combination of the brain images of different subjects which is necessary to form the experimental groups. Thus, groups were made with the averaged data of the BOLD signals of voxels of region-of-interests (ROI) which were located inside each BG of each subject [11,12]. The identification of ROIs representing each center was carried out independently by two researchers with experience in the identification of BG centers in MRI studies (their ability was verified by reproducibility analyses). Functional and anatomical studies were obtained in a single session and with the head fixed in the same position to facilitate a stable relationship between the fcMRI and structural voxels. Subjects who moved during the recording session were also excluded (4 PD-patients and 2 controls). Different structural markers were jointly used to decide where to place each ROI in the brain of each subject [12]. All data sets were normalized to Talairach space.

2.3. Data preprocessing

Data were preprocessed (BrainVoyager software) with a slice scan-time correction, a 3D-motion correction, and a temporal filtering (0.009Hz high-pass GLM-Fourier filter). No spatial smoothing was performed, and studies with a brain-translation > 0.5 mm or a brain-rotation > 0.5° were rejected. Residual motion artifacts and physiological signals (respiration, cardiac activity) were diminished by regressing the BOLD-signals with the mean average of the BOLD-signals recorded in white matter and brain ventricles [16].

2.4. Correlation methods

fcMRI was computed with the average BOLD-signal of voxels included in each ROIs. Thus, the behavior of each BG was represented by the average BOLD-value of all the voxels that make up the ROI, an average which was calculated successively for each of the 400 time-points of the fcMRI study. Values of right and left brain centers were grouped together [17] and, in order to prevent the effect of block transitions, the volumes 1 to 5 and 95 to 100 of all blocks were not included in the correlation analysis. The Pearson correlation coefficient (r; $p < 0.001$ two-tailed) was used to estimate the "strength" of the functional connectivity of the BG centers (Statistica-Statsoft, Tulsa). Partial correlations were used to eliminate the collateral influence of the other BG (used as "regressors") on the functional connectivity between two particular centers [9,10]. Thus, when the interaction between two centers was studied, their BOLD activity was regressed with those recorded in all the other BG. This method is particularly useful in closed-loop networks where the activity of any center may have time-relationships with the activity of all the other centers of the network.

The motor-task effect and the PD effect on the interaction between two centers were considered to be significant when the change of the partial correlation computed for their BOLD-signals reached statistical significance. Differences between two correlation coefficients were identified by using the r-to-Fisher-z transformation ($r' = 0.5*(\ln(1 + r) - \ln(-r)$; r' *being the Fisher-z transformed r)* and a two-sided *t* comparison (*mean and standard error of each sample evaluated against the t distribution with df = n1 + n2–4 degrees of freedom; n1 and n2 being the sample sizes*) adjusted for multiple comparisons [18] (see also essup File2). To prevent false-positive findings when comparing two correlations: 1. the BOLD-values of each subject were normalized as a percentage of their mean value (thus decreasing the effect of the inter-subject variability on the group comparisons), 2. data outliers (> 2*sigma) were withdrawn (so that they did not influence the correlation coefficient), and 3. only comparisons with $p < 0.0001$ were considered as having statistical significance.

3. Results

Table 1 (esupp File 3) shows the position and size of the ROIs used to characterize the BOLD activity of BG and M1. The location of the mean-center of each ROI showed no statistical differences between control subjects and PD patients. Some BG displayed a positive correlation of their BOLD-oscillations (**synchrony**), others displayed a negative correlation of their BOLD-oscillations (**anti-synchrony**), and others showed non-significant BOLD-correlations (**independent** oscillations). Fig. 1 shows the partial correlation between BG (synchrony in red, anti-synchrony in blue, and no functional relationships in black).

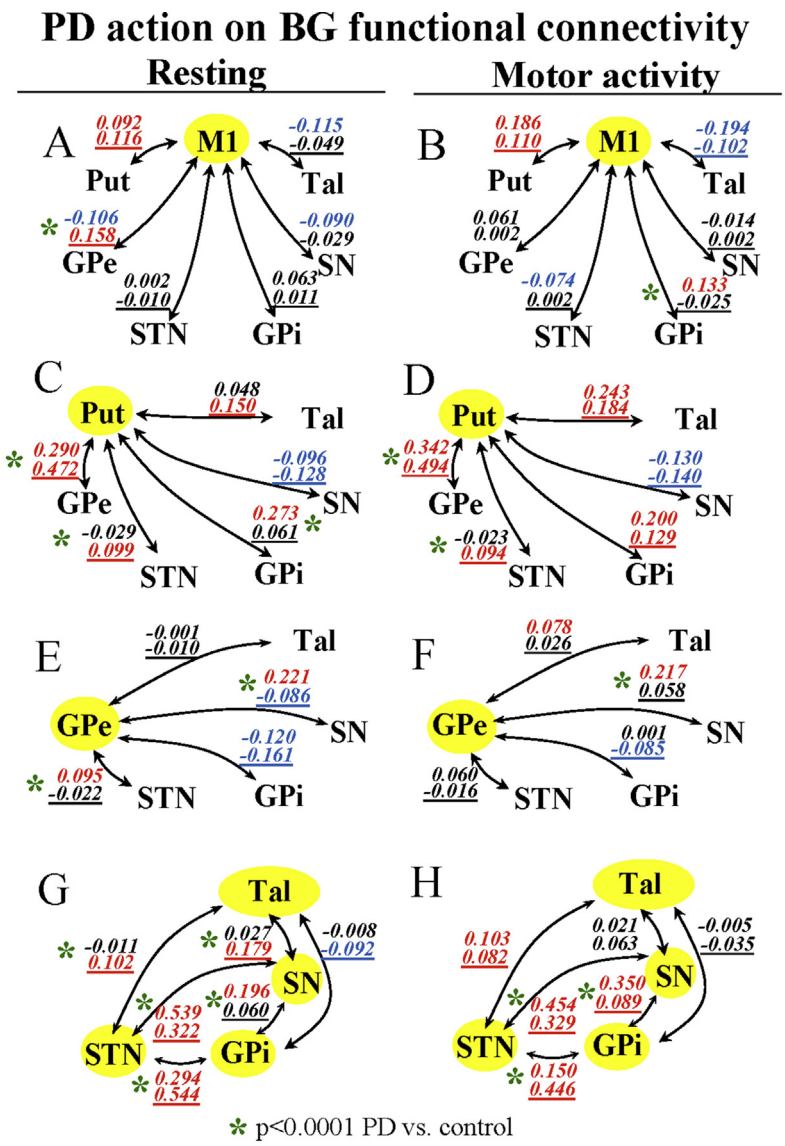

Fig. 1. The influence of PD on the functional connectivity between basal ganglia during resting and finger movements. Diagrams show the partial correlation coefficient during the resting (left-hand side) and finger-motion (right-hand side) intervals. Numbers in red indicate positive correlations, in blue negative correlations and in black no statistical correlations. Statistical differences between the correlation computed in controls and PD patients are shown by an asterisk ($p < 0.0001$). The relative interaction of the M1 with each BG was studied with the multiple linear regression shown at the bottom (I), where red numbers indicate statistical values. STN: subthalamic nucleus, Put: post-commissural putamen, GPe: external globus pallidum, GPi: internal globus pallidum, SN substantia nigra, and Tal: motor thalamus. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

There are two numbers associated to each arrow, the top-position number indicating the correlation coefficient (**r**) in the control group and the bottom-position number (underlined number) indicating the r in the PD-group. Diagrams on the left-hand side show the connectivity computed during resting, and diagrams on the right-side show the connectivity computed during the motor activity intervals.

In the control-group, **M1** showed M1-Put synchrony and M1-GPe, M1-SN and M1-Tal anti-synchrony during resting (Fig. 1A). M1-SN and M1-Tal anti-synchrony was not observed in the PD-group and the M1-GPe anti-synchrony found in the control-group was replaced by a synchrony in the PD-group(Fig. 1A). During the motor-task, the control-group showed M1-Put and M1-GPi synchrony and M1-STN and M1-Tal anti-synchrony(Fig. 1B). M1-Put synchrony and M1-Tal anti-synchrony was also observed in the PD-group, which however did not present either M1-GPi synchrony or M1-STN anti-synchrony. BG proved to be significant predictors of M1 activity, a fact indicated by the multiple linear regressions shown in Fig. 1I (significant predictors in red).

The **Putamen** (Put), in the control-group, showed a positive correlation with the GPe, and GPi, and a negative correlation with the SN (Fig. 1C). Patients showed higher Put-GPe synchrony and lower Put-GPi synchrony than controls. PD patients also showed Put-STN and Put-Tal synchrony which were not found in the control-group. Similar differences between the control-group and PD-group were found during the motor task (Fig. 1D), although under this experimental condition, the control-group showed Put-Tal synchrony and the PD-group showed Put-GPi synchrony.

In the control-group, **GPe** showed synchrony with the STN and SN, and anti-synchrony with the GPi (Fig. 1E). Compared with the control-group, PD patients showed a decrease of GPe-STN synchrony and a reversion of GPe-SN synchrony which was replaced by an anti-

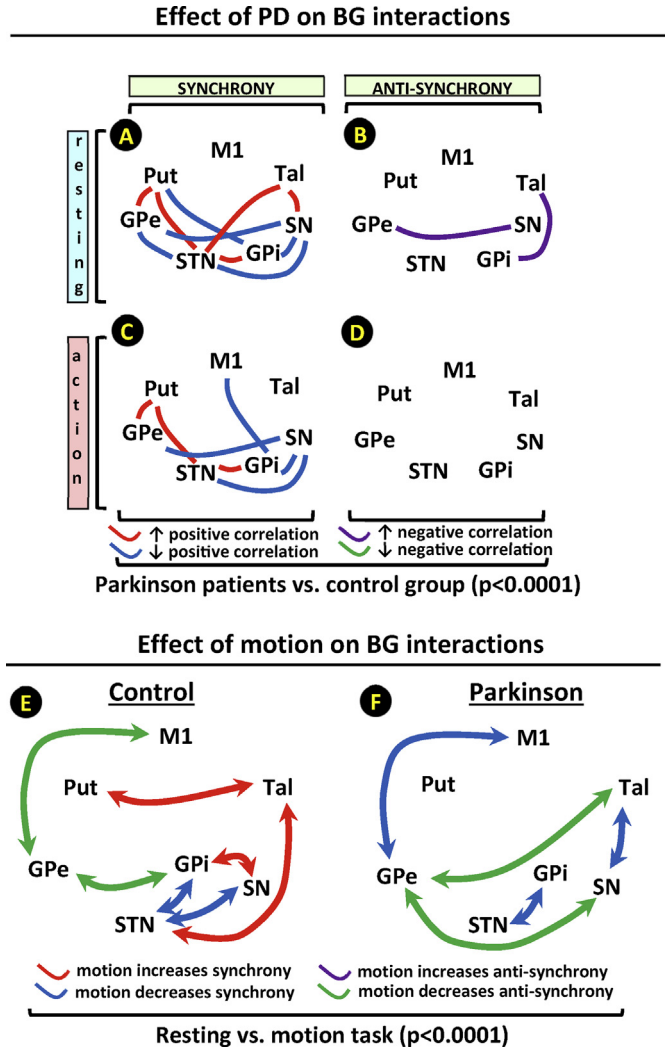

Fig. 2. A summary of the effect of PD on the functional interaction of BG (top) and of the influence of motor activity on these interactions (bottom). In figures A–D the statistical ($p < 0.0001$) differences between PD patients and controls are shown with colored lines. An increase of positive correlations in PD patients (vs. control group) is shown with red lines, an increase of negative correlations with purple lines, a decrease of positive correlation with blue lines and a decrease of negative correlations with green lines. The bottom figures show the influence of the motor-task on the functional connectivity of BG in controls (E) and PD-patients (F). The statistical ($p < 0.0001$) increase of the positive correlation between two centers is shown with red arrows, the decrease of the positive correlation is shown with blue arrows, and the decrease of negative correlations with green arrows. M1: primary motor cortex, STN: subthalamic nucleus, Put: post-commissural putamen, GPe: external globus pallidum, GPi: internal globus pallidum, SN substantia nigra, and Tal: motor thalamus. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

synchrony. During the motor task, the control-group showed GPe-SN and GPe-Tal synchrony which were not observed in PD-patients, and PD-patients showed GPe-GPi anti-synchrony which was not observed in the control-group (Fig. 1F).

The control-group showed, during the resting intervals, a marked **STN** synchrony with the GPi and SN, (Fig. 1G). Regarding controls, STN-GPi synchrony increased and STN-SN synchrony decreased in PD patients, and similar differences were found during the motor tasks (Fig. 1H).

In the control-group, the **GPi** showed synchrony with the SN during the resting and motor task intervals (Fig. 1G/1H). In PD patients, GPi-SN synchrony decreased in both experimental conditions (Fig. 1G/1H).

No functional connectivity was found between the **SN** and the Tal in the control group. PD patients showed SN-Tal synchrony during resting (Fig. 1G) but not during the motor-task (Fig. 1H). Fig. 2 top shows a summary of synchrony (left-side) and anti-synchrony (right-side) differences between controls and PD-patients during both the task-resting (A/B) and the motor-task (C/D).

Thus, BGmC behaved as a **resting-state network** which works during task-resting, but also as a **task-positive network** which changes its activity with particular tasks. Fig. 2 bottom shows the effect of motion on the BG connectivity in both controls (E) and PD patients (F). Red arrows indicate a synchrony increase with motion, blue arrows indicate a synchrony decrease with motion, and green arrows indicate an anti-synchrony decrease with motion (relationships which did not change with motion were not included in the figure). In control subjects, motion increased Put-Tal, STN-Tal and GPi-SN synchrony, decreased STN-GPi and STN-SN synchrony, and decreased M1-GPe and GPe-GPi anti-synchrony (Fig. 2E). The effect of motion was different in PD-patients, where it decreased both M1-GPe, STN-GPi and SN-Tal synchrony and GPe-Tal and GPe-SN anti-synchrony (Fig. 2F).

4. Discussion

fcMRI data showed a complex BG-M1 functional connectivity which changed with motion. PD patients exhibited a severe modification of BG connectivity during both resting and motor task. fcMRI provides information which cannot be obtained by other procedures in humans, and which may help to understand the mechanisms involved in PD motor disorders.

4.1. BG models and fcMRI

The classical BG-model is mainly based on the short-term excitatory-inhibitory interactions between successive centers of the BG-loop and, although it has proved useful to justify different motor disorders in PD, key facts such as why Tal [19] or GPe [20] lesions do not result in bradykinesia, or why GPe lesions do not result in dyskinesia [4], cannot be explained with this model. The classical BG-model assumes that the direct and indirect pathways provide go and no go pointers for motion control, which does not explain why both are activated during actions [5], why the stimulation of the indirect pathway may generate movements [6], and why the stimulation of the direct pathway may inhibit movements [21]. These and other mismatches have encouraged the study of BG from other methodological approaches, one of which is fcMRI.

fcMRI does not provide information about the structural and electrophysiological relationships of brain centers. The functional connectivity between two nuclei can be facilitated by other “crossing nuclei” able to transmit the information between each other, which is particularly feasible in BG whose nuclei are linked by closed-loop circuits. Although most of the functional connectivity data obtained by fcMRI agreed with previous structural data, this method should be considered as an unreliable procedure to establish or to rule out structural connections between BG. In addition, the synchronous/anti-synchronous fluctuations of two nuclei do not necessarily imply their inter-connection by excitatory/inhibitory pathways and, therefore, fcMRI does not provide direct information about the excitatory/inhibitory relationships which are at the basis of the classical BG-model. Functional relationships between two centers of a closed-loop circuit may be influenced by the dynamic of other centers of the circuit, which may hinder the study of the functional connectivity of BGmC centers with fcMRI. This obstacle was addressed here with partial correlation [9,10]. Despite the above commented methodological constraints, fcMRI provides information which may facilitate the understanding of the global dynamics of BG and which cannot be extrapolated from structural or electrophysiological data. The in-phase BOLD-fluctuation of two centers (positive correlation; synchrony) suggests their

functional collaboration. The anti-phase BOLD-fluctuation of two centers (negative correlation; anti-synchrony) suggests that they are involved in different networks with incompatible activities. Centers without a significant correlation are involved in different networks which may work in parallel. This basic interpretation of fcMRI data [8] has proved useful to segregate the motor-loop from the other cortico-BG loops [22], and to identify the somatotopic distribution of the motor BG-loop [23]. However, some limitations of correlation methods (e.g. they assume that BOLD-signals present a normal distribution and a stationary behavior and do not have non-linear components) may generate false-positive findings. Thus, the present results should be considered as preliminary results until they are confirmed by other analytical methods. See more extensive comments about the advantages and limitations of fcMRI methods in esupp File 2 and esupp File 4.

4.2. Functional connectivity of basal ganglia in PD

Some changes in BG-connectivity (Fig. 2A) are compatible with the idea that PD increases indirect pathway activity and decreases direct pathway activity (e.g. PD increased Put-GPe synchrony and decreased Put-GPi synchrony), which is based on the classical model of BG and that has been widely used to explain the motor disorders of PD. Although the therapeutic effects of GPi and STN lesions in PD [24,25] have been considered as the consequence of the reduction of the preponderance of the indirect pathway, this preponderance may only be part of the mechanisms involved in parkinsonian motor disorders. PD patients here showed a number of alterations in different BG-interactions which could also be involved in the motor disorders of these patients. Regarding controls, during the task-resting PD-patients showed increased synchrony of the M1-Put/Put-GPe/Put-STN/STN-GPi/STN-Tal/SN-Tal interactions, and decreased synchrony of the Put-GPi/GPe-STN/GPe-SN/GPi-SN interactions. It could be worthwhile to study the effects of GPi and STN lesions on these other BG interactions, and to analyze the association of these changes with the therapeutic response. The STN showed synchrony with the SN and GPi whose intensity agrees with the density of the structural pathways between these centers [26,27]. STN-GPi synchrony increased and STN-SN synchrony decreased in PD patients, which could also be associated with the better therapeutic response to GPi lesions [28] than to SN lesions [29].

According to the classical BG-model, the disturbance of M1 activity is the immediate predictor of the onset of PD motor disorders, with the low activity of the thalamo-cortical glutamatergic pathway being the trigger for M1-depression and motor disorders in PD. However, present data indicate a complex functional connectivity of M1 with most BG, which suggests that the firing rate of the thalamo-cortical neurons is not the only variable explaining the M1-activity, and that perhaps other variables such as the firing-code of BG-neurons [30] may be relevant. Studies aimed at establishing the influence of the functional connectivity of each BG with M1 on the different PD motor disorders may help understand the basis and control the motor expression of this BG illness.

The effect of motion on the functional connectivity of basal ganglia: differences in PD.

The effect of the motor-task was different in controls and PD-patients. Regarding controls, PD-patients during the motor-task showed the same increase of Put-GPe/Put-STN/STN-GPi synchrony and the same decrease of GPe-SN/STN-SN/GPi-SN anti-synchrony observed in the control-group. However, the increase of STN-Tal/SN-Tal synchrony, the increase of GPe-SN anti-synchrony, and the decrease of Put-GPi/GPe-STN synchrony observed in PD-patients compared to controls during the resting intervals were not found during the motor intervals. This change was induced by the different way in which the motor-task reconfigured the BG interactions in controls and PD-patients (Fig. 2E and F). In the control-group, the motor-task increased Put-Tal/STN-Tal/GPi-SN synchrony, decreased STN-GPi/STN-SN synchrony and decreased M1-GPe/GPe-GPi anti-synchrony. However, the motor-task decreased M1-GPe/STN-GPi/SN-Tal synchrony and decreased GPe-SN/GPe-Tal anti-synchrony in the PD-group. These data show that PD induces complex changes in the BG interactions that are dependent on the task which is being executed. Some of these changes could be involved in the motor disorders which appear when patients start a motor action (e.g. bradykinesia) or which are present during motor-resting (e.g. hypertonia). The consequence of each of the functional reconfigurations of BG for the main PD motor disorders needs further study aimed at comparing the BG reconfiguration of patients with different motor handicaps and under different experimental conditions.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was performed with the approval of the local Institutional Human Studies Committee. This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of interest

Authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.02.031.

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