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Deep brain stimulation of the pedunculopontine tegmentum and subthalamic nucleus: Effects on gait in Parkinson's disease

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ABSTRACT

Objective: This study examines the effects of subthalamic nucleus (STN) deep brain stimulation (DBS) and pedunculopontine tegmentum (PPTg) DBS in advanced Parkinson's disease using gait analysis.
Methods: Five people underwent bilateral DBS in both the STN and PPTg. Gait analysis was performed one year after neurosurgery using an optoelectronic system. The effects of DBS (STN, PPTg and STN + PPTg) were studied in two clinical conditions: without (Off) and during (On) antiparkinsonian therapy.
Results: PPTg and STN DBS were associated with changes in spatio-temporal and kinematics variables.
Conclusions: Although experimental data cannot be generalized widely due to the small sample, PPTg DBS appears to affect the neuronal circuits subserving gait.

1. Introduction

The observation of Masdeu et al. [1] that a patient was unable to stand and generate stepping after a haemorrhage in the tegmentum of the posterior midbrain suggests that the pedunculopontine nucleus (PPN) [2] is involved in human locomotion. Other reports indicate that PPN disorders contribute to gait and postural disturbances in PD [3,4]. It is known that the PPN influences descending inputs from the globus pallidum (GPi), the subthalamic nucleus (STN), and the substantia nigra (SN) [5]. Because these structures are markedly disrupted in Parkinson's disease, their projection to the brainstem motor area may be dysfunctional [5,6].

Deep brain stimulation (DBS) of the basal ganglia is argued to reduce the abnormal activity of the nuclei and improve the functioning of several pathways impaired in PD [7]. Although the STN is considered to be the best DBS target for reducing extrapyramidal symptoms in severe PD, some symptoms, such as gait and dysarthria, do not always respond well to STN DBS [8]. A study by Stefani et al. [9] showed that PPTg DBS affects gait and balance. Moro et al. [10] reported that unilateral stimulation of the PPN was associated with a reduction in falls. In the present study, we carried out gait analysis in people with PD using PPTg and STN DBS to investigate the effects of each nucleus on gait.

2. Subjects and methods

Five hospitalized advanced rigid-akinetic idiopathic PD subjects (five men) who had disabling axial signs and poor LD responses for gait and balance were recruited for this study. The size of the sample was determined by the number of people with PD who were being followed up one year after neurosurgery. Eight age-matched healthy people with no history of neurological or orthopedic diseases and no gait disorders (two women, six men) served as controls (Table 1). Exclusion criteria for PD subjects were the following: (i) presence of systemic or metabolic diseases; (ii) uncertain or unclear history of responsiveness to L-dopa treatment; (iii) presence of brain lesions or marked cortical and subcortical atrophy on brain CT and MR scans; (iv) dementia diagnosed by a clinical examination, or a Mini Mental State Examination score of <24 [11]. All subjects underwent DBS at the Alesini Neurosurgical Hospital in Rome. The surgical procedure has been described in detail elsewhere [9]. Electrode implantation (Medtronic 3389) was performed simultaneously in two target areas of each hemisphere using the "Maranello" double arch system [9]. For STN, the angle in the sagittal plane was 80–85° and in the coronal plane 75–80° to obtain an extra-ventricular and an extra-capsular trajectory. The coordinates for STN were: 11–12 mm lateral to the midline of the third ventricle at CA-CP/2, 4 mm below CA-CP.

According to Stefani et al. [9], it is not possible to establish a fixed-angle range in the sagittal plane for PPN because of high inter-individual variability. The key landmark for minimizing surgical risks is the floor of the IV ventricle (parallel to the brainstem axis). Hence, the trajectory was parallel to the floor of the IV ventricle. Some authors suggest that better coordinates for PPN (actually for PPTg) [12] might be −5/−9 lateral to the midline, 13 mm below PC and about 2 mm behind PC. The definitive choice of the most sensitive value (x coordinate) can also vary depending on the patient's brainstem anatomy [13,14], the width of the cisterna ambient, and the location of the cerebral posterior artery with respect to these structures [9]. In this regard, we are aware of the scientific debate over the precise targeting of PPN [9,15–17] and the difficulty of identifying homogeneous anatomical parameters in this region due to intra- and inter-variability of the anatomical structures [18]. A recent review confirmed that the stimulation target should be the caudal pontine representation of the PPN. This is the pedunculopontine tegmentum nucleus (PPTg)

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Table 1
Clinical features of Control and PD subjects. Extrapyramidal symptoms rated by UPDRS Part III (means and SD).

		Age (years)	Symptom duration (years)	Therapy duration (years)	LTTS[a] (years)
Control	2F/6M	62.0 ± 12.0			
PD	5M	57.8 ± 8.8	16.0 ± 10.0	13.6 ± 8.4	12.8 ± 8.4

Stimulus condition			UPDRS Part III				UPDRS Part III	Items 27–30
THER	STN	PPTg	UPDRS	SD	Items 27–30	SD	%[b]	%[b]
Off	Off	Off	67.6	4.72	12.40	0.55		
Off	Off	On	43.0	9.30	5.60	3.29	35.8	55.3
Off	On	Off	30.0	3.74	3.80	1.64	55.6	69.7
Off	On	On	31.4	8.73	3.20	1.30	53.9	74.2
On	Off	Off	37.4	9.79	4.80	2.59		
On	Off	On	24.6	9.07	2.60	2.30	34.8	53.8
On	On	Off	19.6	5.68	2.60	1.95	46.1	45.9
On	On	On	13.0	6.63	2.40	1.14	65.1	73.1

[a] Long-term treatment syndrome.
[b] Percentage of symptom reduction assessed by UPDRS Part III and items 27–30, between Off stimulation and different stimulus conditions.

[18], not the PPN. After surgery, the definitive electrode locations were verified by brain MRI or CT scans.

2.1. Patient evaluation and study design

Following surgery, stimulation parameters were optimized to reduce disability, as evidenced by the UPDRS Part III. Optimization took place during several visits over the next 3 months. At the time of the study, each patient's stimulus pulse width and frequency were 90 μs and 185 Hz for the STN and 60 μs and 25 Hz for the PPTg. The STN was stimulated using a monopolar stimulation with intensity varied from 1.5 to 2.4 V. The PPTg was stimulated using bipolar stimulation with intensity varied from 1.5 to 2 V. The study was conducted at least one year after neurosurgery and following 30 days of stable antiparkinsonian therapy (levodopa mean daily dosage: 500 mg + peripheral levodopa-decarboxilase inhibitor) and steady electrical parameters during hospitalization at the Santa Lucia Foundation for clinical follow-up and rehabilitation. In the On drug condition (THER On), gait analysis was performed 2 h after the first daily dose of standard medication. Evaluations in the THER On condition were made according to a fixed sequence (STN On PPTg On, STN Off PPTg On, STN On PPTg Off, STN Off PPTg Off) by analyzing each brain stimulation condition on one of four consecutive days. To avoid subjecting participants to additional stress, all Off drug conditions were performed on the same day. Gait analyses were performed in the same sequence as in the THER On condition. In the morning they were performed at least 12 h after the last antiparkinsonian therapy. Gait analysis was performed using the equipment and procedures developed at the motion laboratory of I.R.C.C.S. Fondazione Santa Lucia, Rome, Italy. This included an optoelectronic system (SMART system®, BTS, Padova, Italy) to measure the three coordinates of 23 retroreflective markers. The technical procedure has been described elsewhere [19]. To position the markers correctly, we used an extended "Davis" protocol [20]. In the standard procedure, the anthropometric measures for each person were taken and 15 retroreflective markers were placed on the pelvis and lower body segments. Extending the marker configuration of the "Davis" mode [20], 23 spherical (10 mm diameter) markers (axial: C7, T12 and S1; right and left: acromion, olecranon, ulnar styloid, anterior superior iliac spine, thigh, external femoral condyle, calf, external malleolus, and second metatarsal head and heel) were attached to the body with double-sided tape. For the calves and thighs only, markers were attached approximately 7–10 cm away from the skin on iron rods. PD subjects were blind as to when gait analysis recording would take place. All participants gave their written informed consent to participate in the study, which was approved by the Local Ethics Committee (CE/FARM.44).

2.2. Gait analysis

Spatio-temporal gait measurements were obtained for a series of straight line walking trials (for more details see Peppe et al. [19]). Participants performed six consecutive gait trials. They received no additional instructions during the recording and needed no physical support. The gait acquisition process involved three steps: (1) gait capture with video cameras; (2) transformation (using tracker software) of 2D acquired data into a 3D model by applying the "Davis" model; and (3) stride analysis using the extended "Davis" protocol [20]. To perform the analysis, we used "SMART" (BTS, Padova, Italy), version 1.10.221.0 software.

2.3. Gait variables

We studied the following spatio-temporal variables: mean velocity (m/s), left and right stride length (mm) and left and right stride phase percentages (stance, swing, and double stance). The range of amplitude for the T12 tilt and each upper and lower limb joint on the sagittal plane, calculated as the difference between the minimum and maximum flexion angles in the stance and swing phases, was measured separately. (For more details on calculation methods see Peppe et al. [19].)

2.4. Statistical analyses

We performed statistical analyses on spatio-temporal and kinematic parameters using non-parametric tests (Kruskall–Wallis, Friedman tests and Wilcoxon matched-pairs tests). The Kruskall–Wallis test was used to compare mean velocity and stride, stance, swing, and double stance, which were measured for the right and left sides for each experimental condition (On–Off therapy, no stimulation, STN, PPTg and STN + PPTg), in PD and Control participants. To analyze variations in gait induced by the different brain stimulation conditions in PD, we considered only mean velocity. We adopted this approach after we found correlations between all of the gait variables measured. For this purpose, we calculated a Cronbach' s alpha index, which is a global measure of the correlation between the different variables used to measure the internal consistency of a set of variables. In interpreting the value of the index, if a strong correlation exists all variables can be considered measures of a single phenomenon or factor. α values of 0.70 or higher are usually considered to represent a good correlation. In the PD subjects all gait variables in all therapy and brain stimulation conditions were strongly correlated (see Table 2). The modifications induced by the different brain stimulations and therapies on a single gait variable could therefore be considered to be representative of the modifications induced in all other parameters measured. For simplicity, we chose mean velocity, which is a single measure for each patient independent from side, as a representative variable.

For each PD patient, we had eight repeated measures of the mean velocity corresponding to the combination of the two therapy conditions (On and Off) with the four stimulation conditions (no stimulation, STN, PPTg and STN + PPTg). These repeated measures were analyzed in three steps:

(1) All eight repeated measures of mean velocity were first analyzed with a non-parametric analysis of variance for repeated measures (Friedman test).
(2) A second Friedman test was carried out separately for the On and Off therapy conditions on the four repeated measures of mean velocity corresponding to the four different conditions of brain stimulation (no stimulation, STN, PPTg and STN + PPTg).
(3) Finally, and only for the therapy condition(s) associated with statistically significant differences of mean velocity in the different brain stimulation conditions, we compared the mean velocity in the different stimulus conditions with the no stimulation condition as reference. This analysis was made with the Wilcoxon test for matched pairs.

The statistical analysis was performed with SPSS for Windows (SPSS Inc, Chicago, IL, USA).

Table 2
Internal consistency (Cronbach's alpha) of spatio-temporal variables for Control and PD subjects for each condition.

Group			Cronbach's alpha
Controls			0.562
THER	STN	PPTg	
Off	Off	Off	0.780
Off	Off	On	0.768
Off	On	Off	0.776
Off	On	On	0.777
On	Off	Off	0.766
On	Off	On	0.782
On	On	Off	0.772
On	On	On	0.757

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3. Results

3.1. Spatio-temporal variables

Table 3 reports the median and 25th–75th quartiles for all variables studied for each of the experimental conditions.

3.2. Comparison between PD and Control subjects

For the Off therapy/Off DBS conditions, a comparison between PD and Control subjects revealed statistically significant differences for all spatio-temporal variables (Table 3 and asterisk). Switching On the PPTg did not modify values significantly. Stimulation of STN resulted in parameter normalization, yet no statistical differences were found in PD compared with Control subjects. Switching On both STN and PPTg confirmed the results obtained for STN On alone. In On therapy, we found no difference between PD and Control subjects for any stimulus condition (Table 3 and asterisk).

3.3. Comparisons between conditions in PD

Mean velocity varied significantly in the different conditions of therapy and brain stimulation (Global Friedman ANOVA, Table 3a). When we considered separately the PD subjects in Off and On therapy, we found that DBS induced statistically significant differences in mean velocity only in the Off therapy condition. When people with PD subjects were in On therapy, DBS was unable to induce any improvement in mean gait velocity. Comparing the effects of the different brain stimulations in PD subjects in Off therapy, we found significant improvement of gait velocity only in association with STN stimulation. As reported in Table 3a, when STN Off/PPTg Off was compared with the other DBS conditions, significant increases in mean gait velocity were found in the STN On/PPTg Off and STN On/PPTg On DBS conditions, but no significant differences were found between these two conditions of brain stimulation.

Likewise, the percentage improvement of extrapyramidal symptoms, in particular, gait and balance (items 27–30), was better when STN and both stimuli were On (see Table 1).

3.4. Comparison between PD and control subjects for kinematic variables

The statistical analysis on kinematic variables was performed as reported above for the spatio-temporal variables. Fig. 1 shows the angle displacement traces (°) on sagittal plane of right and left hip and knee for the control group and each PD subject in Off and On therapy and all DBS conditions. The kinematic variables were studied separately in the stance and swing stride phases. As we found no statistical differences in the On therapy condition, we report only the analyses performed in the Off therapy condition. In the stance stride phase, Off therapy/Off DBS revealed significant differences in all kinematic variables except T12 tilt (Table 4a, first column on the left), whereas in the swing stride phase, only the right and left ankle angles were not statistically significant (Table 4a, fifth left column). Switching On PPTg did not greatly modify values in either the stance or the swing phases; on the contrary, On STN alone and On DBS normalized 7 of the 11 variables studied in the stance and swing stride phase.

3.5. Comparisons among different experimental conditions in PD subjects

As shown in Table 4b significant differences in PD subjects in Off DBS and various On DBS conditions made it possible to perform the Wilcoxon matched-pairs test. When we compared Off DBS in both

Table 3
Median (25th and 75th quartiles in parentheses) spatio-temporal variables for Control and PD subjects for each condition. Statistical analyses were performed using the Kruskall–Wallis test ($p < 0.05$).

	Mean Vel (m/s)	R Stride (m)	R Stance (%)	R Swing (%)	R Dblst (%)	L Stride (m)	L Stance (%)	L Swing (%)	L Dblst (%)
Control	1.03 (0.9–1.1)	1.09 (0.9–1.2)	62.9 (62.3–63.5)	36.7 (35.7–37.6)	13.9 (12.5–14.4)	1.09 (0.8–1.2)	63.6 (63–63.7)	36.4 (36.3–37)	13.4 (12.5–14.9)
Off therapy									
STN Off PPTg Off	*0.54 (0.2–0.9)	*0.56 (0.38–0.90)	*67.7 (65–82.2)	*32.3 (17.8–34.9)	*16.1 (14.1–41.2)	*0.57 (0.38–0.90)	66.3 (63–78.2)	33.7 (22.1–37)	18.3 (13.9–18.9)
STN Off PPTg On	*0.84 (0.6–1)	*0.94 (0.6–1)	*64.8 (63.4–69.3)	*35.2 (30.7–36.6)	*17.6 (15–20.3)	*0.94 (0.6–1)	*68.2 (65.2–70.5)	*31.8 (29.5–34.8)	14.6 (13.4–20.1)
STN On PPTg Off	1.05 (0.9–1.1)	1.09 (0.82–1.15)	64 (61.7–65)	36 (35–38.3)	14 (12.5–15.1)	1.1 (0.82–1.14)	64 (62.3–64.9)	36 (35.1–37.7)	14.1 (12.8–15.1)
STN On PPTg On	1.07 (0.7–1.19)	*1.09 (0.67–1.11)	61.3 (60.2–69)	38.6 (30.9–39.8)	12.5 (10.7–15.5)	*1.08 (0.67–1.14)	64.4 (60–65.7)	35.6 (34.3–40)	12.1 (9.5–19.5)
On therapy									
STN Off PPTg Off	0.99 (0.8–1.1)	*1.01 (0.84–1.14)	*64.5 (63.5–65.4)	35.5 (34.6–36.5)	*15.2 (14.6–15.7)	*0.99 (0.82–1.14)	*65.3 (63.8–65.7)	*34.7 (34.3–36.2)	14.5 (14–15.1)
STN Off PPTg On	1.03 (0.8–1.1)	*1.11 (0.81–1.2)	*64.5 (63.8–65.5)	35.5 (34.5–36.2)	14.6 (12.8–15.9)	*1.10 (0.82–1.2)	65.4 (63.8–65.9)	34.6 (34.1–36.2)	15.1 (14–16.5)
STN On PPTg Off	1.05 (1–1.1)	*1.15 (1.03–1.2)	63.9 (62–64.3)	36.1 (35.7–38)	13.3 (12.4–16)	*1.12 (0.8–1.2)	64.1 (62.8–65)	35.9 (35–37.2)	14.1 (13.1–14.3)
STN On PPTg On	1.09 (1.0–1.2)	*1.17 (1.07–1.21)	64.3 (62.3–65.6)	35.7 (34.4–37.7)	13.2 (11.2–16.9)	*1.18 (1.07–1.25)	63.1 (61–66.1)	36.8 (33.9–39)	13.7 (12.4–14.7)

Mean Vel, R/L stride: m/s and m respectively. Stride phases (L/R Stance, Swing, Doublestance: Dblst): percentage (%).
* $p < 0.05$.

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Table 3a
Mean velocity for PD subjects in each experimental condition. Statistical analyses were performed using the Friedman ANOVA and the Wilcoxon matched-pairs test ($p < 0.05$).

	Global	Therapy Off	Wilcoxon test			
			STN Off PPTg Off	STN Off PPTg On	STN On PPTg Off	STN On PPTg On
Mean velocity	0.003	0.012	ns	ns	0.043	0.043

Global: Friedman analysis performed without considering stimulation and therapy; Therapy Off: Friedman analysis performed only Off therapy; Wilcoxon test: statistical analysis performed comparing PD subjects Off stimulation in the different stimulus conditions.

stance and swing phases, we found significant differences only in the On STN-PPTg condition (stance phase: right and left arm 0.043; swing phase: right hip 0.030, left hip 0.043, left arm 0.043), confirming the additional effect of PPTg On STN.

4. Discussion

This study shows the positive effects of bilateral basal ganglia DBS on kinematics and spatio-temporal gait variables in a small

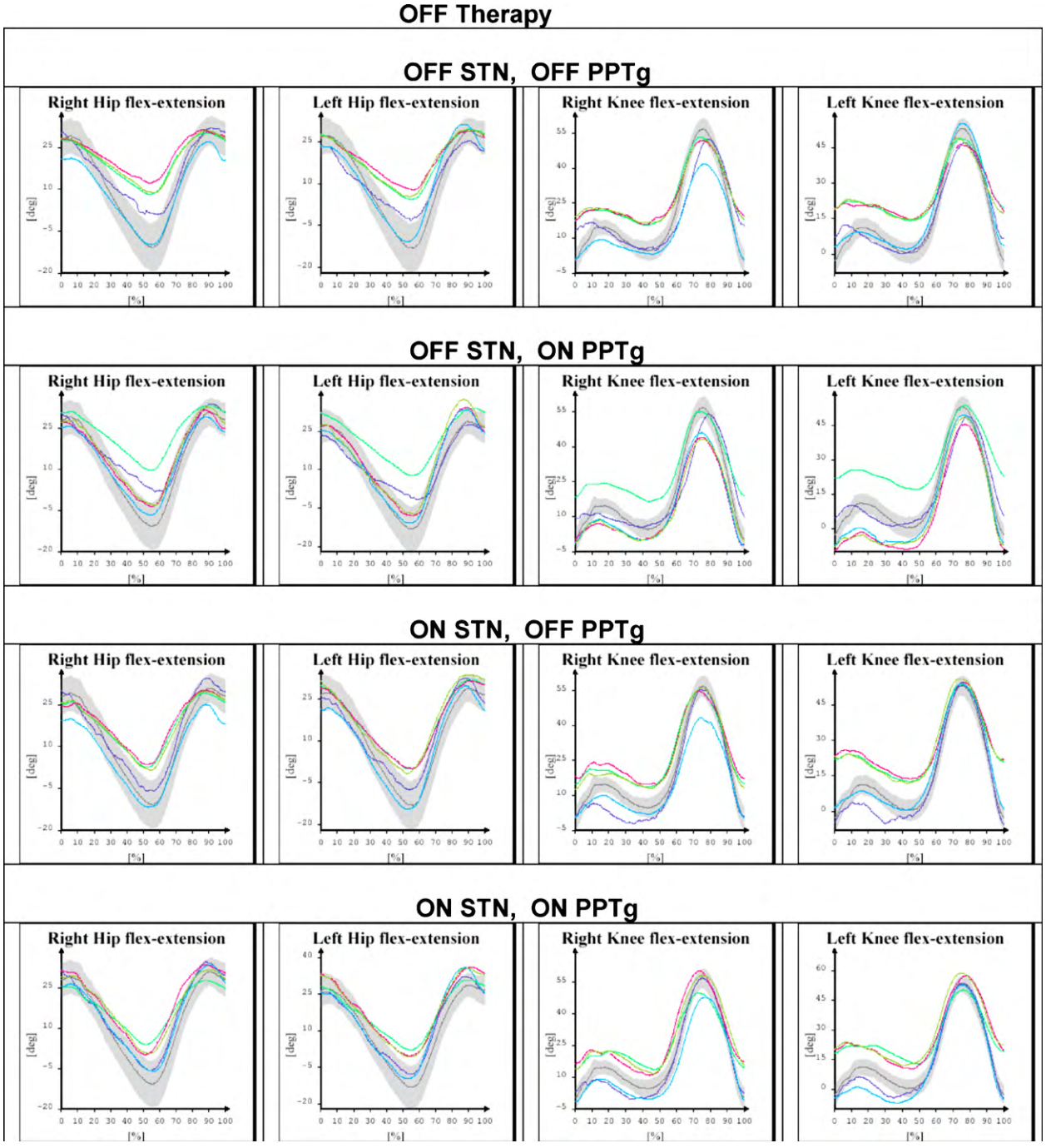

Fig. 1. Angle displacement (°) for the sagittal plane of the right and left hip and knee for the control group and each PD subject in Off and On therapy and all DBS conditions.

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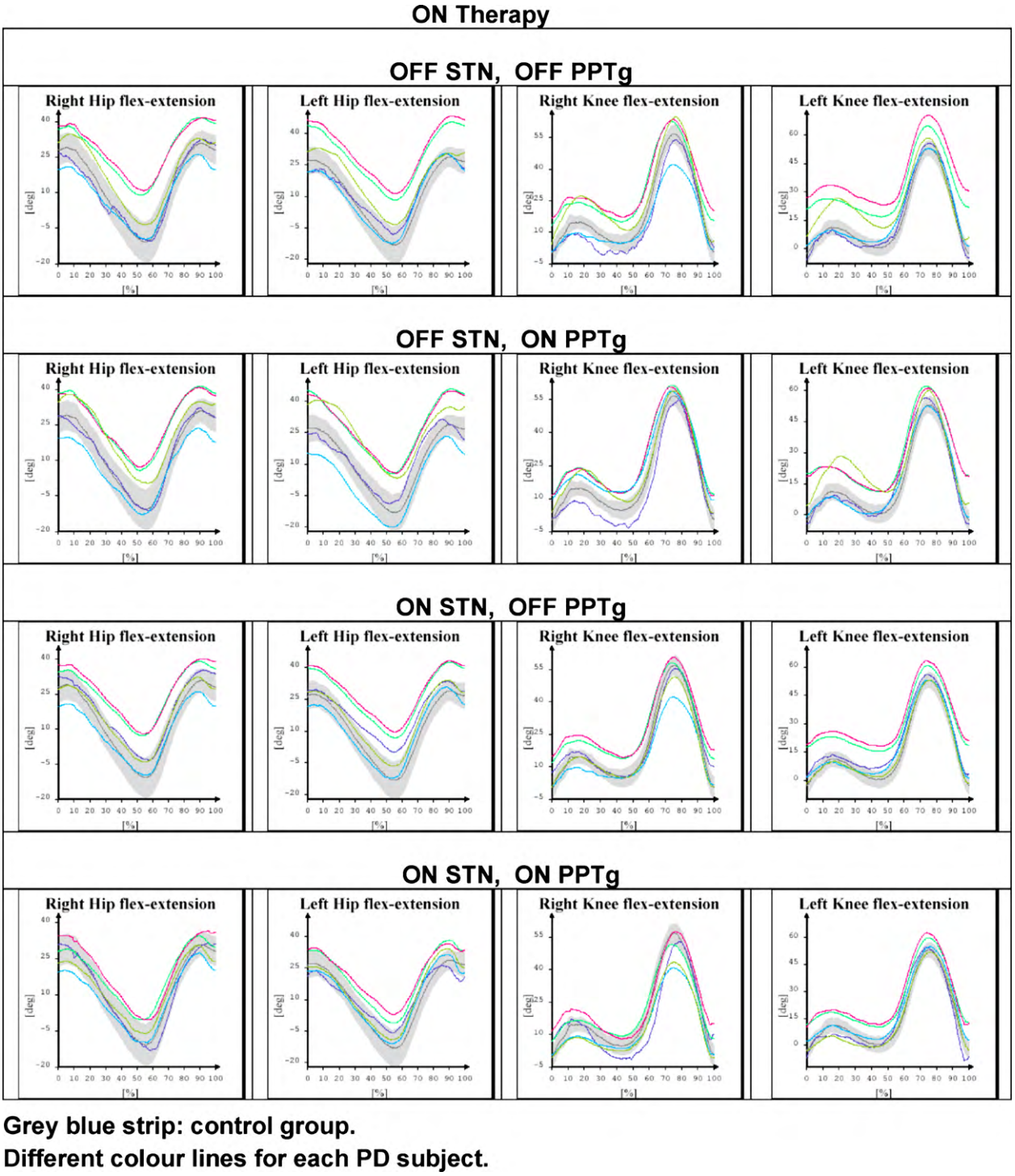

Fig. 1. (*Continued*).

number of people with PD. Testing was carried out using gait analysis, which is an objective and reliable tool for evaluating gait disorders. Several studies have highlighted the efficacy of gait analysis in revealing abnormalities in parkinsonian gait [21]. The efficacy of gait analysis for detecting changes in gait induced by STN DBS [22] is always known. Nevertheless, the efficacy of STN DBS on the gait of PD subjects is still being debated [23]. Faist et al. [24] reported that the efficacy of STN-DBS was comparable to that of levodopa therapy. However, Stolze et al. [25] reported that the effects of STN DBS on gait were not comparable to those of levodopa and that the drug might actually augment the action of STN DBS in an additive manner. Morris et al. [26] proposed that the inconsistent effects of STN DBS on gait might have implications for understanding the physiopathology of gait hypokinesia in PD. They proposed that the main deficit was stride length control, which is regulated by the basal ganglia. They also suggested that cadence might be regulated by locomotor regions at the midbrain or spinal levels [27]. Of all the midbrain structures, the PPN, together with its tegmentum (PPTg), is the one most involved in postural, balance and gait regulation mechanisms [28]. Important projections descend from this structure to both the spinal cord and the brainstem [28].

A careful review of the available literature on mammalian PPN suggests that the nucleus is a heterogeneous structure devoted to

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Table 4a
Angular variables for Control and PD subjects in the stance and swing stride phases in the Off therapy condition. Statistical analyses were performed using the Kruskall–Wallis test ($p < 0.05$).

	Off therapy							
	Stance				Swing			
	STN Off PPTg Off	STN Off PPTg On	STN On PPTg Off	STN On PPTg On	STN Off PPTg Off	STN Off PPTg On	STN On PPTg Off	STN On PPTg On
Right								
T12tilt	ns	ns	ns	ns	0.040	ns	ns	ns
Ankle	0.007	0.003	ns	ns	ns	ns	ns	ns
Knee	0.028	ns	ns	ns	0.008	ns	ns	ns
Hip	0.002	0.020	0.019	0.006	0.003	0.005	ns	ns
Arm	0.008	0.040	ns	ns	0.003	0.019	0.003	0.010
Elbow	0.019	0.008	0.013	0.008	0.008	0.013	0.019	0.040
Left								
Ankle	0.003	ns	ns	ns	ns	ns	ns	ns
Knee	0.020	ns	ns	ns	0.003	0.005	ns	ns
Hip	0.010	0.040	0.040	0.019	0.008	0.019	0.008	0.019
Arm	0.013	0.013	ns	ns	0.003	0.008	ns	ns
Elbow	0.003	0.028	0.019	0.019	0.019	ns	ns	ns

Kinematic variable of right and left leg (hip, ankle and knee), arm (arm and elbow), trunk (T12 tilt) considered separately in the stance and swing stride phases.

Table 4b
Off therapy: kinematic variables for PD subjects in each experimental condition.

	Stance		Swing	
	Global	Ther Off	Global	Ther Off
Right				
T12tilt	ns	ns	ns	ns
Ankle	0.013	0.048	ns	ns
Knee	0.036	ns	ns	ns
Hip	0.009	ns	0.026	0.050
Arm	ns	0.020	ns	ns
Elbow	ns	ns	ns	ns
Left				
Ankle	0.022	ns	ns	ns
Knee	ns	ns	0.040	0.041
Hip	0.044	ns	0.022	ns
Arm	0.012	0.021	0.030	ns
Elbow	0.003	0.026	ns	ns

Kinematic variable of right and left leg (hip, ankle and knee), arm (arm and elbow), trunk (T12 tilt) considered separately in the stance and swing stride phases; Global: Friedman analysis performed without considering DBS stimulation and therapy; Therapy Off: Friedman analysis performed Off therapy.

not just motor functions [15–17]. For instance, specific subportions might be involved in the modulation of spinal cord excitability [12], whereas others likely affect sleep, associative domains, or even reward [12,29–31]. Our data show that compared with the Off DBS condition, On PPTg DBS and On STN DBS increased of mean walking velocity. Bilateral combined switching of both targets induced statistical differences primarily in motion, spatio-temporal and kinematic variables. Therefore it seems that both nuclei act synergistically. Nevertheless, the effects of PPTg DBS alone do not appear to be as dramatic as those of STN DBS alone. When people with PD were tested after they took their chronic daily dopaminergic therapy, we found that gait was improved by L-dopa in Off DBS. Switching On STN, PPTg, or both stimuli did not lead to further improvements in these subjects.

These findings 12 months after surgery during chronic Levodopa therapy are in agreement with previous clinical data reported by Stefani et al. [9] on bilateral DBS and by Moro et al. [10] on unilateral brain stimulation. In our study, consistent and prolonged effects on parkinsonian symptoms were seen, confirming the involvement, of the PPTg On motor circuits. In order to continue in-depth examination of the mechanisms involved in gait and the changes that occur in PD, extensions of this research are required.

Conflicts of interest

The authors have no conflicts of interest.

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