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ORIGINAL COMMUNICATION

Postural instability and gait disorders after subthalamic nucleus deep brain stimulation in Parkinson's disease: a PET study

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Abstract

Introduction Patients with Parkinson's disease sometimes report postural instability and gait disorders (PIGD) after subthalamic nucleus deep brain stimulation (STN-DBS). Whether this is the direct consequence of DBS or the result of natural disease progression is still subject to debate.

Objective To compare changes in brain metabolism during STN-DBS between patients with and without PIGD after surgery.

Methods We extracted consecutive patients from a database where all Rennes Hospital patients undergoing STN-DBS are registered, with regular prospective updates of their clinical data. Patients were divided into two groups (PIGD and No PIGD) according to changes after surgery, as measured with a composite score based on the selected Unified Parkinson's Disease Rating Scale items. All patients underwent positron emission tomography with ^{18}[F]-fluorodeoxyglucose 3 months before and after surgery. We ran an ANOVA with two factors (group: PIGD vs. No PIGD; and phase: preoperative vs. postoperative) on SPM8 to compare changes in brain metabolism between the two groups.

Results Participants were 56 patients, including 10 in the PIGD group. The two groups had similar baseline (i.e., before surgery) characteristics. We found two clusters of increased metabolism in the PIGD group relative to the No PIGD group: dorsal midbrain/pons, including locomotor mesencephalic region and reticular pontine formation, and right motor cerebellum.

Conclusion We found different metabolic changes during DBS-STN among patients with PIGD, concerning brain regions that are already known to be involved in gait disorders in Parkinson's disease, suggesting that DBS is responsible for the appearance of PIGD.

Keywords Parkinson's disease · Subthalamic nucleus deep brain stimulation · Gait disorders · Positron emission tomography with ^{18}[F]-fluorodeoxyglucose

Introduction

Deep brain stimulation of the subthalamic nucleus (STN-DBS) in Parkinson's disease alleviates DOPA-sensitive symptoms, including rigidity, akinesia and tremor. There is sometimes late development of gate problem after STN-DBS, about 5 years, which could be explicated by natural history of Parkinson's disease [1]. More rarely, patients develop postural instability and gait disorders (PIGD), including lack of balance and freezing of gait, earlier after STN-DBS: freezing for 11/123 (8.9%) patients at 1 year after surgery in one study [2], and freezing for 35/147 (23.8%) patients and balance disorders for 44/147 (29.9%) patients at 2 years after surgery in another study [3]. This raises a question concerning the possibility of causal link between surgery and these early gait disorders.

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Freezing is correlated with postural inability and may share common mechanisms, although the exact basis for these two complex phenomena remains unknown [4]. Studies of Parkinson's disease using animal models or functional brain imaging techniques have shed some light on the structures involved in the control of locomotion and gait disorders. These structures can be summed up as frontal and parietal cortical areas [5–7], and more especially the supplementary motor area and right superior parietal lobule [8], basal ganglia [7], cerebellar locomotor region [9], and supraspinal structures such as the mesencephalic locomotor region (MLR) [10, 11] including the pedunculopontine nucleus (PPN) and pontine reticular formation.

The main consequence of PIGD is falls, which can have a severe impact on quality of life. This is why the potential role of the STN-DBS in their appearance needs to be clarified, with a view to possibly improving the selection procedure for this surgery.

We hypothesized that STN-DBS brings about a specific modulation of neural circuits in patients who develop PIGD after surgery. To support this idea, we studied changes in brain metabolism before and after surgery in patients with Parkinson's disease, using positron emission tomography with ^{18}[F]-fluorodeoxyglucose (PET-FDG). Our main objective was to compare metabolic changes between patients with and without DOPA-resistant PIGD after surgery, to ascertain whether it can be attributed to STN-DBS.

Methods

Participants and clinical assessment

We extracted patients from a database where all Rennes Hospital patients undergoing STN-DBS are systematically registered, with regular prospective updates of their clinical data. More specifically, we extracted consecutive patients from August 2004 to October 2015 who had undergone PET-FDG 3 months before and after surgery. All patients met the criteria of the Parkinson's UK Brain Bank for idiopathic Parkinson's disease. They were selected for bilateral STN-DBS if they had disabling levodopa-induced symptoms refractory to medical treatment, disease lasting more than 5 years, and if they were under 70 years old. All patients were free from DOPA-resistant axial motor signs (including PIGD), cognitive decline (Mattis Dementia Rating Scale score < 130 and absence of major executive deficits), and psychiatric disturbance. We excluded patients whose imaging was not usable, or who had a neurological comorbidity that might interfere with their symptoms. Patients underwent a full clinical assessment 3 months before and 1 year after surgery. This included Part III of the Unified Parkinson's Disease Rating Scale (UPDRS) in an OFF-medication state (no medication for at least 12 h before the test) and best ON-medication state (best motor state following the usual morning dose of levodopa enhanced by 50 mg of levodopa), as well as in OFF- and ON-stimulation conditions after surgery. Parts I, II and IV were also administered. Rennes University Hospital Institutional Review Board approved the study. Written informed consent was obtained from all participants.

Composition of patient groups

To divide the patients into the two groups, one with PIGD after surgery (PIGD group) and one without (No PIGD group), we calculated a composite gait score used in the literature [12], by summing Items 14 and 15 ("freezing" and "gait") of the UPDRS-II (activities of daily living) and Items 29 and 30 ("postural stability" and "gait") of the UPDRS-III (motor examination). Patients were assessed in the ON state, so as to only consider DOPA-resistant manifestations, 3 months before and 1 year after surgery. A change of less than 2 points (total score of 16 points) was not considered clinically relevant [12], but if the score had increased by at least 2 points 1 year after surgery (worsening), patients were placed in the PIGD group. We waited until 1 year after surgery [2] to ensure that the patients' response to DBS had stabilized, and because we considered that this was too short an interval for any clinical changes to be due solely to natural disease progression. We also calculated the PIGD score 3 months after surgery, at the time of the postoperative PET-FDG scan.

Neurosurgery

Quadripolar DBS electrodes were bilaterally implanted in the STN using the stereotactic method. The locations of the selected electrode contacts were determined using stereotactic coordinates derived from a 3D CT scan.

PET-FDG procedure

Patients underwent PET-FDG 3 months before and after surgery. Assessments were performed at the Nuclear Medicine Unit of Rennes University Hospital (France). We followed the same procedure as that described by Auffret and colleagues with DBS patients [13]. Patients underwent a resting-state 18F-FDG-PET scan after fasting, on medication. Glucose levels were controlled before injecting the 18F-FDG. PET measurements were performed using a dedicated Discovery ST PET scanner (GEMS, Milwaukee, WI, USA) in 2D mode, with an axial field of view of 15.2 cm. A 222–296 MBq injection of 18F-FDG was administered

intravenously under standardized conditions (quiet, dimly lit room, eyes and ears open, head holder). A crosshair laser system was used to ensure stable and reproducible positioning. A 20-min 2D emission scan was performed 30 min post-injection, with patients positioned at the center of the field of view. X-ray CT-based attenuation correction was performed prior to the emission scan. Following scatter, deadtime and random corrections, PET images were reconstructed by means of 2D filtered back projection, yielding 47 contiguous transaxial 3.75-mm thick slices.

PET data analysis

The data were analyzed with Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London) written in MATLAB version 7.9.0 (MathWorks, Natick, MA, USA). All images were realigned using affine transformation and were then spatially normalized to a standard stereotactic space (Montreal Neurological Institute (MNI) template). Finally, images were smoothed, using an isotropic 12-mm full width at half maximum isotropic Gaussian kernel to ensure normal distribution and respect parametric statistics assumptions.

We defined three regions of interest (ROIs), based on the structures identified in the literature as being potentially involved in gait disorders (see "Introduction"). These regions were frontal and parietal cortical areas for the cortical level, putamen–striatum–STN for the basal ganglia level, and midbrain–pons–anterior cerebellum for the infratentorial level. We used the Talairach Daemon database atlases [14] from the WFU PickAtlas toolbox [15] implemented in SPM8.

Statistical analysis

To identify brain regions whose metabolic changes with STN-DBS differed between the two groups of patients, we ran a 2 (group: PIGD vs. NO PIGD) × 2 (phase: before vs. after surgery) analysis of variance (ANOVA) on SPM8, looking for a Group × Phase interaction. Results were considered to be significant at $p < 0.05$ after familywise error (FWE) correction at peak and cluster level. We ran the analysis for each ROI. To compare the baseline characteristics of the two groups, we used the Mann–Whitney nonparametric test.

Results

Patients' characteristics

We included 56 patients, 10 in the PIGD group and 46 in the No PIGD group (Fig. 1). Their clinical characteristics are provided in Table 1. The two groups were clinically similar before surgery, with the same disease duration and same clinical stage in terms of motor and cognitive

Table 1 Patients' characteristics

	PIGD	No PIGD	*p**
Number of patients (%)	10 (18%)	46 (82%)	
Number of men (%)	4 (40%)	26 (56%)	0.43
Mean age in years ± SD	58.2 ± 8.5	56.9 ± 6.7	0.71
Mean disease duration in years ± SD	11.9 ± 2.7	11.0 ± 4.1	0.39

PIGD postural instability and gait disorders, *SD* standard deviation

*$p < 0.05$ (Mann–Whitney)

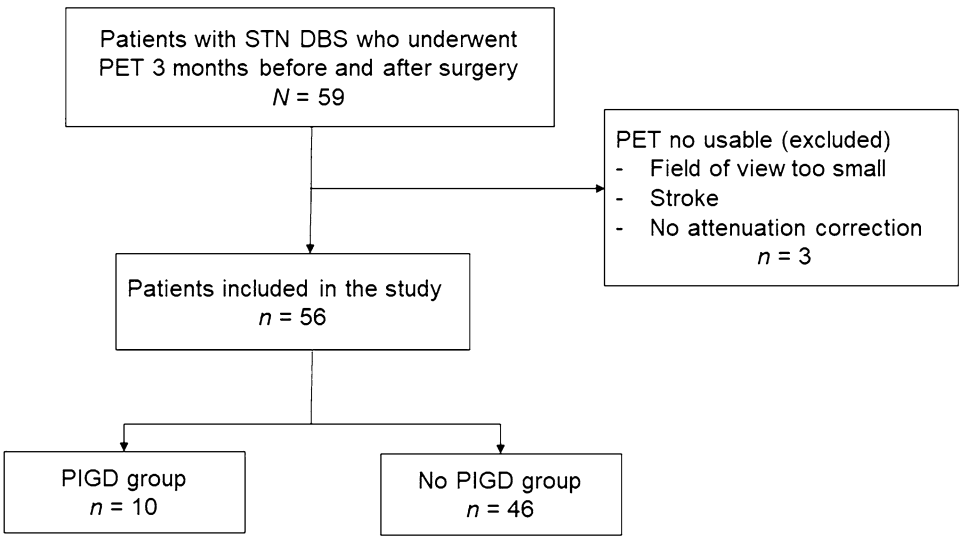


Fig. 1 Flowchart. *STN-DBS* subthalamic nucleus deep brain stimulation, *PET* positron emission tomography, *PIGD* postural instability and gait disorders

impairment. 1 year after surgery, we noted a significant difference in UPDRS-III scores in ON-medication-ON-DBS state between the two groups (11.4 ± 6.6 in the PIGD group versus 6.4 ± 4.9 in the No PIGD group, $p = 0.04$) (Table 2). This could be explained by the fact that two items from the UPDRS-III were included in the composite score used to divide the patients into the two groups. The PIGD score 3 months after surgery in ON-medication-ON-DBS state was also higher in the PIGD group (1.4 ± 0.8 vs. 0.7 ± 0.9; $p = 0.02$). Concerning the stimulation parameters (Table 3), we found a significant difference between the groups on voltage on the right side (mean = 2.8 ± 0.4 vs. 2.2 ± 0.7, $p = 0.01$). This difference was also significant for the total electrical energy delivered (TEED) [16] ($p = 0.01$). It should be noted that data concerning the electrode contact coordinates were missing for 25 patients, including four patients in the PIGD group.

Table 3 Deep brain stimulation parameters at 3 months

	PIGD	No PIGD	p*
Mean voltage ± SD (in mV)			
Right	2.8 ± 0.4	2.2 ± 0.7	**0.01**
Left	2.5 ± 0.5	2.2 ± 0.7	0.14
Mean frequency ± SD (in Hz)	140.5 ± 17.6	130.9 ± 3.7	0.09
Mean pulse width ± SD (in µs)	63 ± 9.5	61.3 ± 6.2	0.79
Mean ± SD *x*/*y*/*z* coordinates of active contacts (in mm)			
Right	14.4 ± 2.1	14.0 ± 2.4	0.67
	− 2.1 ± 2.1	− 3.5 ± 1.5	0.11
	− 1.25 ± 3.4	− 1.2 ± 3.0	0.71
Left	− 14.3 ± 1.6	− 14.3 ± 1.4	0.90
	− 3.0 ± 2.7	− 3.8 ± 1.4	0.46
	− 2.3 ± 1.7	− 1.4 ± 2.1	0.46

Bold value indicates statistical significant values ($p < 0.05$ Mann–Whitney)

x/*z* = with respect to the anterior commissure–posterior commissure (AC–PC) line, *y* with respect to the midpoint of the AC–PC line

PIGD postural instability and gait disorders, *SD* standard deviation

*$p < 0.05$ (Mann–Whitney)

ROI analysis

We found a significant Group x Phase interaction, indicating that changes in brain metabolism after surgery differed between the two groups, but only for the infratentorial ROI (midbrain-pons-anterior cerebellum). Metabolism increased significantly after surgery in two clusters for the PIGD group, relative to the No PIGD group. The first cluster (Fig. 2) included the dorsal pons and most of the MLR, which contains the PPN. The second cluster (Fig. 2) included the right motor cerebellum. We did not find any cluster where metabolism decreased significantly after surgery in the PIGD group. On the strength of the significant interaction, we studied the simple effect of each factor [17] to confirm the direction of our finding. When we compared the preoperative and postoperative phases within each patient group, we found a significant difference in metabolism (Fig. 3). However, no significant difference emerged when we compared the two groups at each phase (i.e., preoperative

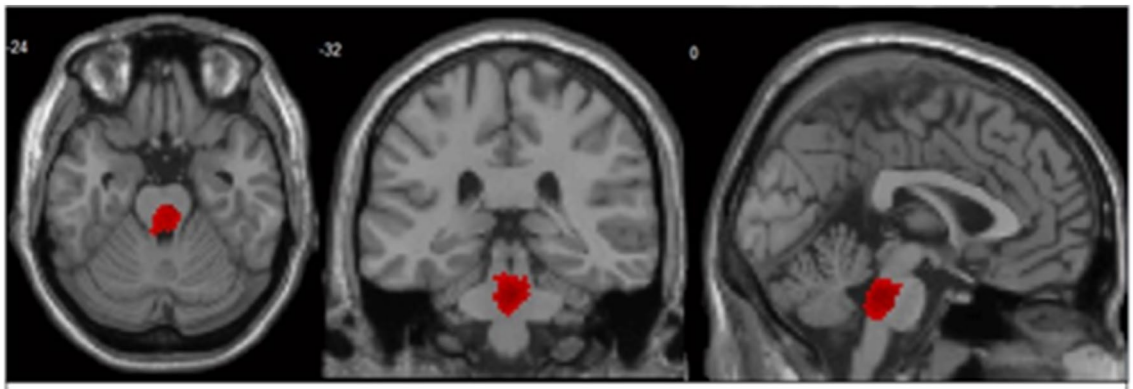
Table 2 Results of clinical assessment

	3 months before surgery			3 months after surgery			1 year after surgery		
	PIGD	No PIGD	p*	PIGD	No PIGD	p*	PIGD	No PIGD	p*
Mean UPDRS-III ± SD									
Med off– DBS off	35.7 ± 14.1	32.3 ± 12.6	0.64	33.7 ± 11.1	31 ± 11.7	0.43	34.3 ± 15.6	35.1 ± 14.1	0.58
Med off– DBS on				21.6 ± 10.8	14.8 ± 9	**0.04**	21.6 ± 8.3	16.9 ± 10	0.15
Med on–DBS off	6.9 ± 4.7	8.7 ± 6.2	0.57	8.9 ± 6.3	10.7 ± 8.1	0.53	15.9 ± 8.9	12.5 ± 7.6	0.27
Med on–DBS on				6.2 ± 3.2	6.0 ± 5.7	0.47	11.4 ± 6.6	6.4 ± 4.9	**0.04**
Mean PIGD score ± SD									
Med off–DBS off	7.3 ± 3.2	5.6 ± 2.5	0.11						
Med off–DBS on				6.1 ± 2.5	4 ± 2	**0.01**	6.4 ± 2.5	4.5 ± 2.7	0.05
Med on–DBS off	0.9 ± 1.0	1.1 ± 1.2	0.73						
Med on–DBS on				1.4 ± 0.8	0.7 ± 0.9	**0.02**	3.4 ± 0.7	0.9 ± 1.0	**< 0.001**
Mean MDRS score ± SD	139.6 ± 2.6	140.6 ± 2.8	0.19	138,7 ± 3,9	139,9 ± 3,4	0.28	139.8 ± 2.8	140.1 ± 3.2	0.65
Mean LEDD in mg/d ± SD	1359 ± 830	1201 ± 567	0.72	870.9 ± 452,2	735,7 ± 464,4	0.45	910 ± 378	706 ± 443	0.65

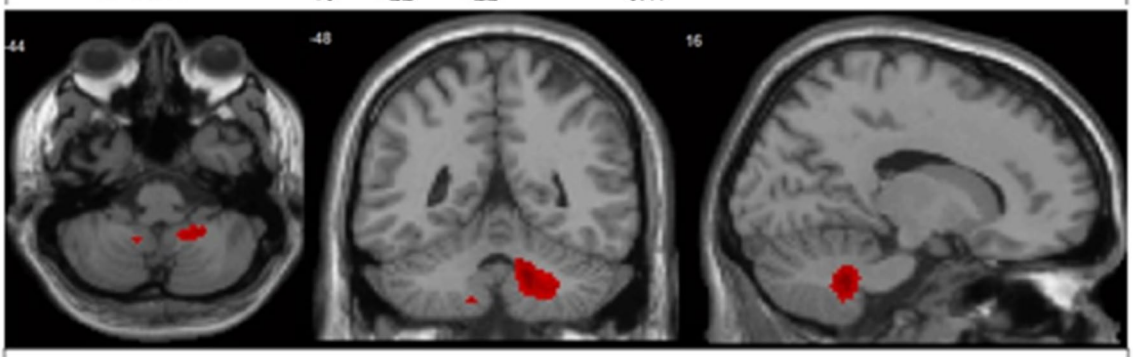
Bold values indicate statistical significant values ($p < 0.05$ Mann–Whitney)

PIGD postural instability and gait disorders, *UPDRS-III* Unified Parkinson's Disease Rating Scale Part III, *MDRS* Mattis Dementia Rating Scale, *LEDD* levodopa equivalent daily dose, *Med* medication, *DBS* deep brain stimulation

*$p < 0.05$ (Mann–Whitney)



Region	MNI coordinates			*p* FWE peak	Cluster size (*n* voxels)	*p* FWE cluster
	x	y	z			
Pons	0	-34	-30	0.04		
	6	-26	-30	0.04	385	0.009
Midbrain	10	-22	-22	0.17		



Region	MNI coordinates			*p* FWE peak	Cluster size (*n* voxels)	*p* FWE cluster
	x	y	z			
Anterior cerebellum (right)	16	-50	-38	0.02	182	0.03

Fig. 2 Clusters in brainstem and cerebellum with increased metabolism after STN-DBS (PIGD group–No PIGD group). Coordinates are given in Montreal Neurological Institute (MNI) space; *FWE* familywise error

and postoperative). Analyses with the other two ROIs failed to yield any significant results.

Discussion

We observed different changes in brain metabolism after STN-DBS among patients who developed DOPA-resistant PIGD after surgery, in two areas of the brain that are already known to be involved in gait and postural control. The first cluster was located in the inferior dorsal midbrain, which notably included the MLR with the PPN, which many MRI [10, 11] and PET [18] studies have identified as a key structure in gait disorders in Parkinson's disease. This cluster also included the dorsal pons (pontine tegmentum), which could be regarded as forming part of the MLR [19] and again is known to be involved in gait and posture [20]. A PET study [18] revealed activation of the pontomesencephalic regions in patients with PIGD in the OFF-medication condition, suggesting a potential compensatory role for these structures. Another PET study found MLR and PPN activation in patients whose gait was improved by STN-DBS, suggesting that DBS modulates these structures [21]. The second cluster was in the motor cerebellum, which could be implicated in PIGD, according to a recent study [9]. In our study, metabolic change was assessed across a relatively short period before and after surgery (3 months). This seemed too short for natural disease progression to bring about metabolic change [22], which is therefore more likely to have been a consequence of DBS. Moreover, we noted that the PIGD

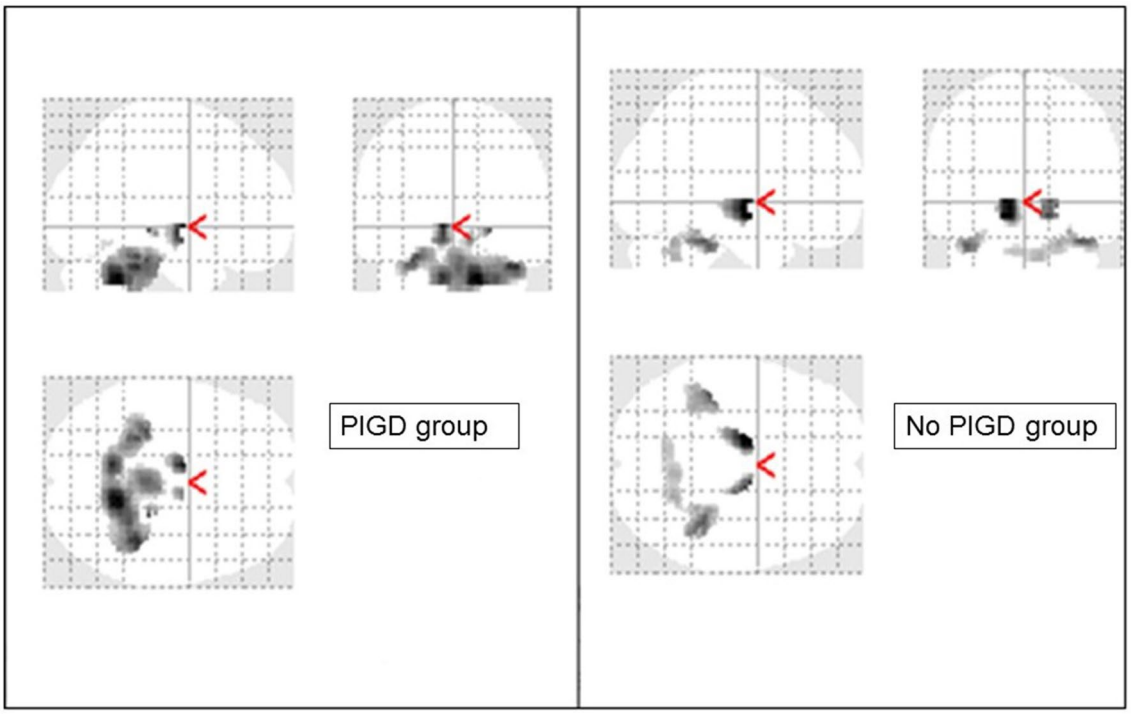


Fig. 3 Results of simple effect analysis given as brainglass, increased metabolism after surgery for each group

score at 3 months after surgery was significantly poorer in the PIGD group, both ON and OFF medication, whereas the two groups had similar scores before surgery, whether patients were OFF or ON medication. This may be additional evidence of the role of DBS, rather than medication.

There are several possible explanations for this differential effect of DBS. First, there is the difference in stimulation parameters between the two groups: the voltage and TEED on the right side was higher in the PIGD group, and an increase in freezing episodes has already been observed among patients with a higher voltage [23]. Another hypothesis is that higher parameters in the PIGD group could reflect a less optimally placement of electrodes which could activate other path. Second, it could have been a difference in the anatomical location of the stimulation electrodes, with DBS having a different effect on walking according to which part of the STN was stimulated [24, 25]. There was no significant difference in our study, but data were only available for 35 patients. Moreover, using coordinate is not the best way to assess contact position because of the anatomic variability. It is more relevant to look at contact position in relation to nucleus, but we had not these data. Third, there could have been a difference in levodopa equivalent dose after surgery, but we found no significant difference between our groups. Fourth and last, patients with PIGD could have been in a more advanced stage of disease, such that DBS had a different effect. However, our patients were all at the same clinical stage before surgery (as shown in Table 1) and we found no difference in brain metabolism before surgery between the two groups in the simple effect analysis. That said, the disease may have been more diffuse in the brains of patients in the PIGD group, involving locomotor structures such as the MLR or pontine reticular formation, at too early a stage to have any impact on either brain metabolism or clinical symptoms. These structures seem to be affected by alpha synuclein accumulation at an early stage of the disease [26]. DBS may, therefore, act as a *trigger* for clinical decompensation and the appearance of gait disorders.

Limitations

First, assessing metabolism and the clinical score at different times (3 months and 1 year after surgery) is obviously a limitation. This was a retrospective study, and our database only contained 3-month PET scans. These scans had been timed to meet the needs of previous studies focusing on other clinical topics, notably apathy [27]. The problem is that 3 months is probably too short an interval for there to be a stable clinical motor response to DBS. Nevertheless, PIGD scores already differed between the two groups 3 months after surgery, albeit less so than 1 year after. Moreover, assessing clinical change later than metabolic change could make sense, insofar as the latter is probably detectable earlier than the former, as has already been seen in other neurodegenerative disorders such as Alzheimer's disease

[28]. There is the same problem for deep brain stimulation parameters that we looked at 3 months, but were different at one year for 15 patients, including 4 patients in the PIGD group. Second, we did not use a recent and more specific scale to assess gait disorders, as no such data were recorded in the database. We nevertheless considered that the UPDRS items remained relevant, having been used in many previous studies on this topic [12, 29]. Third, we only had a small number of patients in the PIGD group, but this reflected the proportion of patients who display gait disorders after surgery, as described in previous studies [2, 3, 30]. Fourth, PET-FDG assessed metabolism in a resting state, and not during a specific activation task. Any difference in metabolism may, therefore, have reflected indirect mechanisms, meaning that results needed to be interpreted with care in terms of pathophysiological hypotheses. Finally, we did not have a control group (similar patients without STN-DBS) with which to compare changes in gait 1 year on. So we cannot definitely confirm the link between surgery and early gait problem.

Perspectives

STN-DBS seems to have an impact on locomotor structures, leading to a worsening of gait a few months later for some patients. But the limitations of our study do not allow us to formally conclude; follow-up longitudinal studies should be performed to confirm our results. Moreover, the nature of the underlying mechanisms remains unclear. The use of a different—and potentially more sensitive—preoperative imaging modality (activation task imaging) to look for potential deficits predictive of gait disorders after surgery might be a relevant means of better selecting candidates for surgery. Studying the electrodes' insertion path among patients with gait disorders after surgery could also be useful for understanding the underlying mechanisms.

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Compliance with ethical standards

Conflicts of interest The authors report no disclosures relevant to the manuscript.

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