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ORIGINAL COMMUNICATION

PPNa-DBS for gait and balance disorders in Parkinson's disease: a double-blind, randomised study

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Abstract Gait and balance disorders are the major source of motor disabilities in advanced forms of Parkinson's disease (PD). Low-frequency stimulation of the pedunculopontine nucleus area (PPNa-DBS) has been recently proposed to treat these symptoms with variable clinical results. To further understand the effects of PPNa-DBS on resistant gait and balance disorders, we performed a randomised double-blind cross-over study in six PD patients. Evaluation included clinical assessment of parkinsonian disability, quality of life and neurophysiological recordings of gait. Evaluations were done 1 month before, 4 and 6 months after surgery with four double-blinded conditions assessed: with and without PPNa-DBS, with and without levodopa treatment. Four patients completed the study and two patients were excluded from the final analysis because of peri-operative adverse events (haematoma, infection). Clinically, the combination of PPNa-DBS and levodopa treatment produced a significant decrease of the freezing episodes. The frequency of falls also decreased in three out of four patients. From a neurophysiological point of view, PPNa-DBS significantly improved the anticipatory postural adjustments and double-stance duration, but not the length and speed of the first step. Interestingly, step length and speed improved after surgery without PPNa-DBS, suggesting that the lesioning effect of PPNa-DBS surgery alleviates parkinsonian akinesia. Quality of life was also significantly improved with PPNa-DBS. These results suggest that PPNa-DBS could improve gait and balance disorders in well-selected PD patients. However, this treatment may be riskier than others DBS surgeries in these patients with an advanced form of PD.

Keywords Parkinson's disease · Deep brain stimulation · Pedunculopontine nucleus · Gait disorders

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Introduction

Gait and balance disorders are the major source of motor disabilities in advanced forms of Parkinson's disease (PD) and are a burden for the patients and their families. They are a cause of high morbidity leading to a large number of minor injuries, fractures and increased nursing home placements, and have been related to mortality [1] as well as high healthcare cost [2]. At present, gait and balance disorders are less or unresponsive to dopaminergic treatment as well as deep brain stimulation (DBS) of the subthalamic nucleus (STN) or internal pallidum [3, 4]. Their physiological basis is poorly understood, but recent data obtained in animal models, healthy volunteers and PD patients strongly suggest a dysfunction of the mesencephalic locomotor region (MLR) containing the

pedunculopontine nucleus (PPN) and the cuneiform nucleus. In monkeys, a specific lesion of PPN cholinergic neurons is sufficient to induce gait and postural deficits [5]. Using fMRI in healthy adults and in PD patients, MLR activation has been observed during mental imagery of gait [6, 7]. Furthermore, in PD patients, PPN cholinergic neurons degenerate progressively over time [8, 9], with a significant correlation between falls and speed of gait and the number of cholinergic neurons in the PPN and the reduction of thalamic acetylcholine concentrations [5, 10–12].

Recently, some teams have proposed and performed low-frequency PPN area-DBS (20–40 Hz) in order to activate the remaining cholinergic neurons and alleviate levodopa-resistant gait and balance disorders in some selected PD patients. PPNa-DBS was first proposed for PD patients previously implanted with STN or zona-incerta DBS in open label trials [13–15]. In these patients, it was shown for the first time that PPNa-DBS can improve not only gait and balance but also parkinsonian symptoms [13–15]. Unfortunately, these results have not been consistently confirmed in double-blind assessments [16]. In PD patients not previously operated for STN-DBS, variable results have been reported with PPNa-DBS, with subjective improvement in the number of falls or freezing episodes [17, 18]. More recently, an objectively measured improvement was finally demonstrated in PD patients during blinded On/Off stimulation comparisons by using specific and precise assessments of freezing of gait (FOG) [19]. Taken together, these results suggest that PPNa-DBS can sometimes reduce gait and balance disorders by 50 % with a long lasting effect for a few PD patients [18], although it remains unclear which selection criteria predict positive outcomes.

The variable clinical results could be explained by different factors. First, advanced PD patients are a heterogeneous population and no parameters that predict a good motor outcome with PPNa-DBS has been identified to date. Second, FOG and falls are difficult to quantify because they are episodic and context dependent [20]. More importantly, there is high variability in terms of the brainstem areas targeted, which have poorly defined boundaries, and for which detailed knowledge of the anatomical projections is unavailable in humans. To date, targeted brainstem areas include the peripeduncular nucleus [14], the PPN [16] or deeper pontine areas [18].

In the present study, we aim to address some of these issues and specifically evaluate the effects of PPNa-DBS in carefully selected and tested PD patients with levodopa-resistant gait and balance disorders. For this purpose, we used a validated method of targeting to precisely implant the electrodes within the PPNa, defined individually for each patient [5, 16], and assessed parkinsonian symptoms and gait and balance disorders by using a combination of specific clinical and neurophysiological approaches [19] in a controlled double-blind randomised trial.

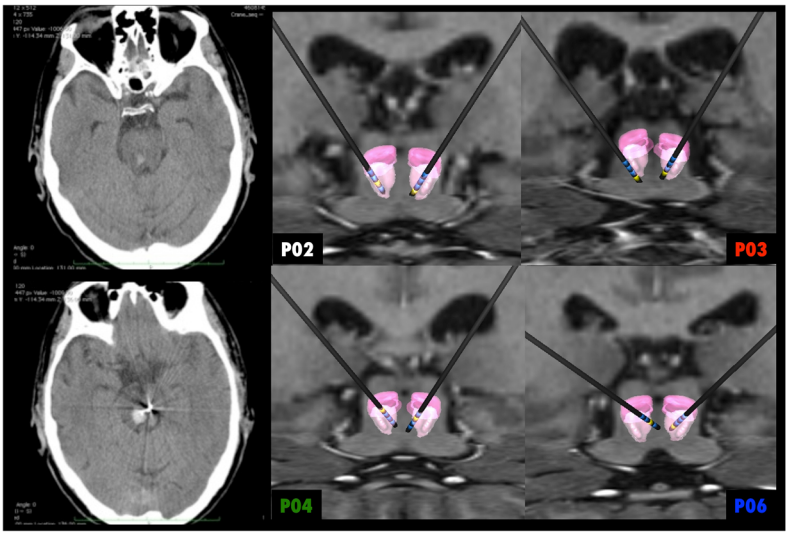
Patients

Six PD patients with dopa-unresponsive gait and/or balance disorders were operated for bilateral PPNa-DBS at the Pitié-Salpêtrière Hospital, Paris (INSERM promotion, C08-07, No. IDRCD/2008-A00324-51, ClinicalTrials.gov Registration NCT02055261). This study received approval from the local ethics committee (CPP, Ile-de-France, Paris VI) and all the patients gave written informed consent to participate. Patients met the following inclusion criteria: (1) age below 71 years, (2) a severe form of PD (Hoehn and Yahr 'Off' drug >2.5) [21], (3) gait and/or balance disorders partly responsive to levodopa treatment, with the items falling (item 13) and/or freezing of gait (item 14) and/or gait (item 29) and/or postural instability (item 30) of the Unified Parkinson's Disease Rating Scale (UPDRS) ≥2 with levodopa treatment ('on' drug) [22], (4) >50 % decrease in others motor symptoms with levodopa treatment, (5) presence of disabling levodopa-induced motor complications despite optimal medical treatment. Exclusion criteria included dementia (Mattis Dementia Rating Scale <129, MDRS) [23], ongoing psychiatric disturbances, surgical contraindications and relevant brain lesions detected on MRI.

Imaging data, surgical procedure and stimulation parameters settings

MRI imaging acquisition (1.5 T) was performed the day before surgery, with a Leksell stereotactic frame in place. The PPNa was targeted using two different methods with (1) direct individual targeting using a 3D deformable atlas of the basal ganglia [7, 16] and (2) calculation of a statistical target as previously reported [24]. The two sets of coordinates were compared and a mean target chosen. Quadripolar electrodes (Model 3389, Medtronic, Minneapolis, MN) were bilaterally implanted and electrode placement was verified using intraoperative radiography [16, 17].

A 3D helical CT-scan was performed after surgery to visualise electrode tracks and determine contact locations and coordinates (Fig. 1) [16, 25]. The contacts coordinates were calculated in millimetres from midline (laterality), ventrodorsal distance (*d*) from floor of the fourth ventricle and rostrocaudal distance (*h*) from a pontomesencephalic line connecting the pontomesencephalic junction to the inferior colliculi caudal margin, as described (− above this line; + below this line) [16, 19].



	Contact	F (Hz)/P (μs)/ A (V)	l (mm)	d (mm)	h (mm)
Right P02	1-2+	40/60/3.1	− 5.6	7.8	− 1.6
Left P02	0-1+	40/60/3.1	3.4	8.7	− 1.4
Right P03	0-	40/60/1.6	− 4.0	10.4	0
Left P03	0-	40/60/1.8	2.7	9.3	− 0.6
Right P04	3-2+	40/60/0.8	− 5.2	9.2	− 5.4
Left P04	2-3+	40/60/1.2	3.2	8.7	− 2.5
Right P06	1-0+	20/60/2.4	− 2.2	7.8	− 4.6
Left P06	0-1+	20/60/1.3	3.6	6.3	− 3.5
Mean ± SD		35 ± 9.3/ 60/ 1.9 ± 0.9	|3.7| ± 1.2	8.5 ± 1.2	− 2.5 ± 1.9

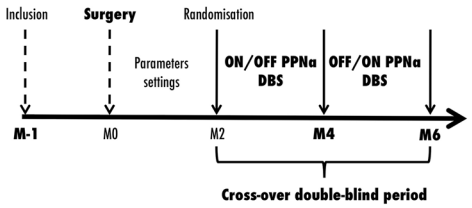


Fig. 1 Electrode locations and design of the study. *Left* Post-operative CT-scan in patient 5, who experienced a midbrain haemorrhage. *Middle* Magnetic resonance images showing the contact locations used for chronic PPN stimulation in the four PD patients. Active contacts are *yellow* (cathode) and non-active or anode contacts are *blue*. Anterior frontal view with 3D atlas reconstruction showing the PPN (*transparent pink*) and the cuneiform nucleus (*solid pink*). *Table* Parameter settings and coordinates of the stimulating contacts used in each patient during the double-blind period. The coordinates are given in millimetres from midline (laterality, − right side, + left side), ventrodorsal distance (*d*) from floor of the fourth ventricle and rostrocaudal distance (*h*) from a pontomesencephalic line connecting the pontomesencephalic junction to the inferior colliculi caudal margin (− above this line; + below this line). *Right bottom* Design of the cross-over randomised double-blind study

After 4 days, the electrodes were connected to the Kinetra stimulator (Medtronic). Clinical effects were checked for each contact (frequency 5–130 Hz; pulse width 60 μs, amplitude 0–5 V). Stimulation parameters were optimised over a 2 month post-operative period and set to below the threshold for side-effects, which were principally paresthesia and oscillopsia (Fig. 1) [16]. The sequence of the stimulation conditions ('Off' versus 'On') for the double-blind cross-over period was individually randomly assigned for two periods of 2 months duration (Fig. 1). Stimulation parameters and medication were constant for at least 4 weeks before each evaluation.

Outcome measures

Patients were evaluated a month before surgery ('Off' and 'On' drug conditions), and 4 and 6 months following surgery ('Off' and 'On' PPNa-DBS according to the randomisation sequence, and 'Off' and 'On' drug conditions) (Fig. 1).

Clinical evaluation

Gait and balance disorders and parkinsonian disability

The Rating Scale for Gait Evaluation (RSGE) was chosen as the main outcome criterion to precisely evaluate gait and balance deficits in PD patients [26]. This scale is multidimensional, and comprised of four parts: (I) functional impairment including falling (item 6), (II) gait/balance side-effects of levodopa treatment including freezing of gait (item 7), assessed by patient interview in both with and without levodopa treatment, (III) socioeconomic impact and part (IV) objective clinical assessment focused on gait and balance evaluated in both the Off state, after a 12-h interruption of antiparkinsonian medication, and in the best On levodopa condition after the administration of a single suprathreshold dose of levodopa.

Parkinsonian disability was evaluated using the UPDRS part II-activities of daily living with patient interview comprising frequency of falls (item 13) and FOG (item 14) subscores in both Off and On levodopa conditions; UPDRS part III-motor disability score with objective clinical assessment comprising the 'axial' subscore (sum of items 18 + 27 + 28 + 29 + 30; i.e. speech, rise from a chair, posture, gait and postural stability) also performed in the Off and best On levodopa status [22].

Parkinsonian quality of life was assessed by interview using the Parkinson's Disease Questionnaire Summary-Index (PDQ-39-SI) [27].

Levodopa-equivalent dosage was also recorded and levodopa-related complications evaluated using the UPDRS part IV [22].

Cognitive and psychiatric status

Neuropsychological evaluation focused on executive functions, attention, memory and visuoconstructive abilities with (1) global efficiency assessed using the MDRS, (2) cognitive auto-activation abilities using the Phonological Fluency test (P in 120 s), (3) reactive flexibility using the Trail Making test, (4) inhibitory control using the Stroop Task, (5) sustained attention and impulsivity using the Continuous Performance test (CPT), (6) verbal learning with the Free and Cued Selective Reminding tests and (7) the visuoconstructive abilities and non verbal memory with the Rey–Osterrieth Complex Figure copying test, visual agnosia being controlled with the overlapping figures [28]. The Comprehensive Psychopathological Rating Scale (CPRS) [29] was used to assess depression (Montgomery and Asberg depression scale—MADRS) and anxiety (Brief Anxiety scale—BAS). Lastly, emotional functions were examined using the recognition of facial expressions (happiness, surprise, fear, disgust and sadness) [30].

Gait initiation walking test

Biomechanical parameters of gait initiation were recorded using a force platform (0.9 m × 1.8 m, AMT Inc. LG6-4-1) [31]. The accelerations and velocities of the centre of gravity (CG) and centre of foot pressure (CP) displacements of the first two steps were calculated in real time.

During the anticipatory postural adjustments (APAs) phase, the period between the first biomechanical event (t_0) and the foot-off of the swing leg (t_{FO1}), the CP posterior and lateral displacements and the duration of APAs were calculated. During step execution, the period between the FO1 and foot-contact (FC), step length (L), step width (W) and peak AP velocity of the CG (V_m) were measured. The vertical CG velocity was also calculated and two values extracted from it: the peak negative value during the swing phase (V_1) and its value at the time of foot contact (V_2). The braking index, which reflects active postural control, was then calculated ($(V_1 - V_2)/V_1 \times 100$) [32]. The double-stance duration ($t_{FC} - t_{FO2}$) was also measured (Fig. 2).

Statistical analysis

The primary endpoint was the change in the RSGE at the end of each stimulation period (M4 versus M6). We determined that to reach a power of 80 % with an alpha risk of 5 %, we had to recruit six patients, given the following hypothesis: (i) five out of six patients would complete the study and (ii) the improvement of RSGE scale with PPNa-DBS would be of 30 %. The Wilcoxon Signed-Ranks test was used to compare the clinical scores and biomechanical parameters of gait obtained at the end of each period, and with baseline status, with respect to the same preoperative drug condition. Statistical analyses were performed using Statview® (Statview Software, USA). The significance level was taken as $p < 0.05$.

Results

Two out of six patients could not complete the study because of severe adverse effects. Patient 1 presented an infection that required removal of the electrodes and stimulator 1 month after surgery. He recovered without sequelae and decided not to be re-implanted. Patient 5 suffered from a centrimetric midbrain haematoma that occurred 72 h after electrodes implantation, before stimulator implantation (Fig. 1). The immediate post-operative period was unremarkable and the CT-scan performed a few hours after surgery revealed no bleeding. The patient's conditions abruptly worsened 72 h later with preserved consciousness, right third cranial nerve palsy, left hemibody hypotonia and increased rigidity of the right side. Four days later, consciousness became impaired, necessitating life support in the intensive care unit. After recovery, he was discharged at home, wheel-chair bound, anarthric and had to be fed with a gastrostomy feeding tube. Thus, only four patients completed the cross-over study (Table 1).

Location of the DBS electrodes

For all the patients, all the electrodes were localized bilaterally within the PPNa according to our method (Fig. 1).

Effects of PPNa-DBS alone on gait and balance disorders compared to PPNa-DBS and before surgery without levodopa treatment

Clinical assessments

Overall, no significant change of the RSGE (Fig. 2) or UPDRS (Fig. 3) scores was found during the double-blind period comparing On versus Off PPNa-DBS, nor when comparing On PPNa-DBS to before surgery (Off drug condition).

Individually, PPNa-DBS alone induced a decrease in the falling (item 6-RSGE) and FOG (item 7-RSGE) subscores in three out of four patients compared to without PPNa-DBS, and a decrease in FOG in three out of four patients compared to before surgery (Fig. 2c, d, Off levodopa). Objective clinical assessment (RSGE-part IV) revealed that gait initiation (item 14), postural stability while walking

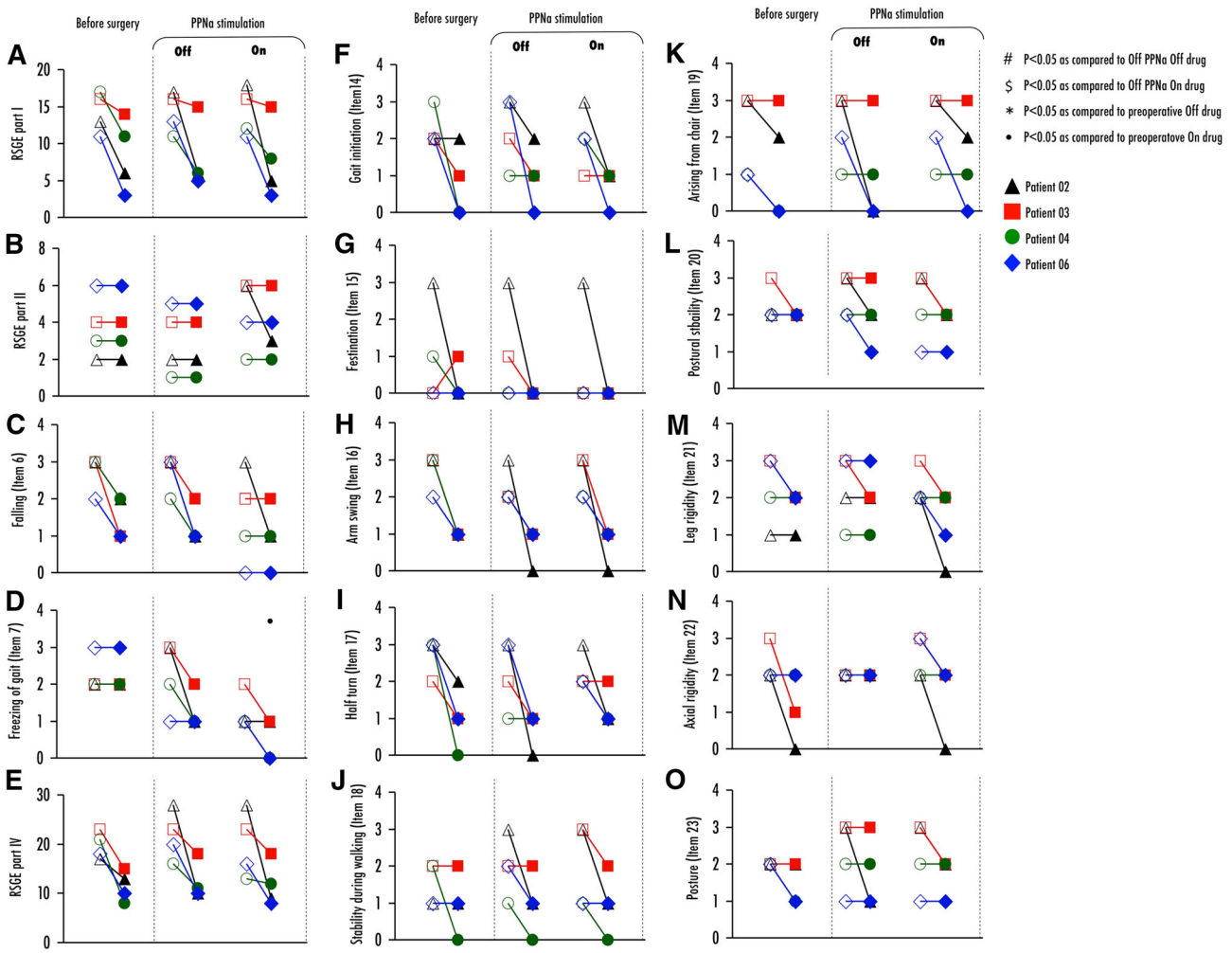


Fig. 2 Effects of PPNa-DBS on Rating Scale for Gait Evaluation (RSGE) in four PD patients. Change in Rating scale for gait evaluation (RSGE) part I (**a**), part II (**b**), falling and freezing of gait subscores (items 6 and 7, **c**–**d**), clinical objective evaluation (part IV, **e**–**o**), with/without PPN-DBS and with/without levodopa treatment. *Each symbol* represents one patient, without (*unfilled*) or with (*filled*) levodopa treatment

(item 18) and posture (item 23) were increased in two patients after surgery in the absence of drug and PPNa-DBS (Fig. 2k, j, o). UPDRS assessments showed that individually, PPNa-DBS alone (Off levodopa) decreased frequency of falls (item 13) in two patients (4 and 6; Fig. 3b), the FOG (item 14) in two patients (3 and 6; Fig. 3c), and reduced the postural instability (item 30) in two patients (3 and 6; Fig. 3f), compared to without PPNa-DBS and before surgery (Off levodopa). Lastly, falling (item 6-RSGE and item 13-UPDRS) and FOG (item 7-RSGE and item 14-UPDRS) subscores were aggravated in one to three patients after surgery, in the absence of drug and PPNa-DBS (Figs. 2c, d, 3b, c).

Physiological parameters of gait and postural control

PPNa-DBS alone ('Off' drug) significantly increased the posterior and lateral CP displacements during the APAs and decreased double-stance duration (Fig. 4). Compared to the preoperative period On levodopa, the combination of PPNa-DBS and levodopa treatment (On stimulation On levodopa) also significantly decreased double-stance duration (Fig. 4).

The length and velocity of the first step were also significantly higher after surgery, independent of PPNa-DBS conditions (Fig. 4).

Table 1 Demographic characteristics of six PD patients operated for bilateral PPNa-DBS

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Gender (age)	M (69)	F (70)	F (68)	F (64)	M (63)	M (46)
Disease duration	19	18	23	10	14	12
RSGE (0–69)						
Off drug	44	39	52	51	33	44
On drug	30	26	41	14	37	19
UPDRS part III (0–108)						
Off	44	45	61	38	38	50
On	18	16	30	19	16	19
UPDRS part II (0–52)						
Off	21	26	28	22	11	22
On	19	9	19	6	11	5
PDQ-39 (0–156)	60	32	86	66	33	65
MDRS (0–144)	132	140	130	141	139	139
MADRS (0–60)	0	7	6	2	2	2
BAS (0–54)	2	6	0	1	0	5
Levodopa-related complications (UPDRS part IV)	4	9	9	4	5	10
Levodopa-equivalent (mg/day)	1700	570	700	1050	585	1300

High scores indicate worse motor or psychiatric signs, except for MDRS for which high scores indicate better cognitive function

BAS Brief Anxiety Scale, *MADRS* Montgomery and Asberg Depression Scale, *MDRS* Mattis Dementia Rating Scale, *PDQ-39* Parkinson's disease quality of life questionnaire, *RSGE* Rating scale of gait evaluation, *UPDRS* Unified Parkinson's Disease Rating Scale

Effects of PPNa-DBS combined with levodopa treatment on gait and balance disorders compared to PPNa-DBS and before surgery with levodopa treatment

Clinical assessments

Overall, no significant change of the RSGE (Fig. 2) and UPDRS (Fig. 3) scores was found during the double-blind period comparing On PPNa-DBS On levodopa versus Off PPNa-DBS On levodopa, nor when comparing to before surgery (On levodopa).

Individually, PPNa-DBS combined with levodopa treatment decreased falling (item 6-RSGE) in three out of four patients compared to without PPNa-DBS or before surgery (On levodopa; Fig. 2c). PPN-DBS combined with levodopa treatment also decreased FOG (item 7-RSGE) in three out four patients compared to without, and in all patients compared to before surgery (On levodopa; Fig. 2d). UPDRS assessments also revealed that the frequency of falls (item 13-UPDRS) and FOG (item 14-UPDRS) subscores decreased with PPNa-DBS combined with levodopa treatment compared to without PPNa-DBS as well as to before surgery (Fig. 3b, c).

Physiological parameters of gait and postural control

Combining the PPNa-DBS and levodopa treatment induced a significant decrease in double-stance duration, compared to before surgery (On levodopa; Fig. 4d) with no significant change in the gait initiation parameters compared to without PPNa-DBS after surgery (Fig. 4).

The length and velocity of the first step were also significantly higher after surgery with levodopa treatment, independent of PPNa-DBS conditions (Fig. 4).

Effects of PPNa-DBS on quality of life, cognition, psychiatric symptoms and levodopa treatment

During the double-blind period, a significant improvement in the quality of life (PDQ-SI; Fig. 3h) was observed with PPN-DBS compared to without PPNa-DBS during the double-blind period and to before surgery.

No significant changes were observed in cognitive, psychiatric or emotional functions after surgery, regardless of PPNa-DBS stimulation condition (Fig. 2g, h; Table 2), except for patient 6 who presented with a major depression 4 months after surgery without PPNa-DBS that improved a few days after switching On the PPNa-DBS.

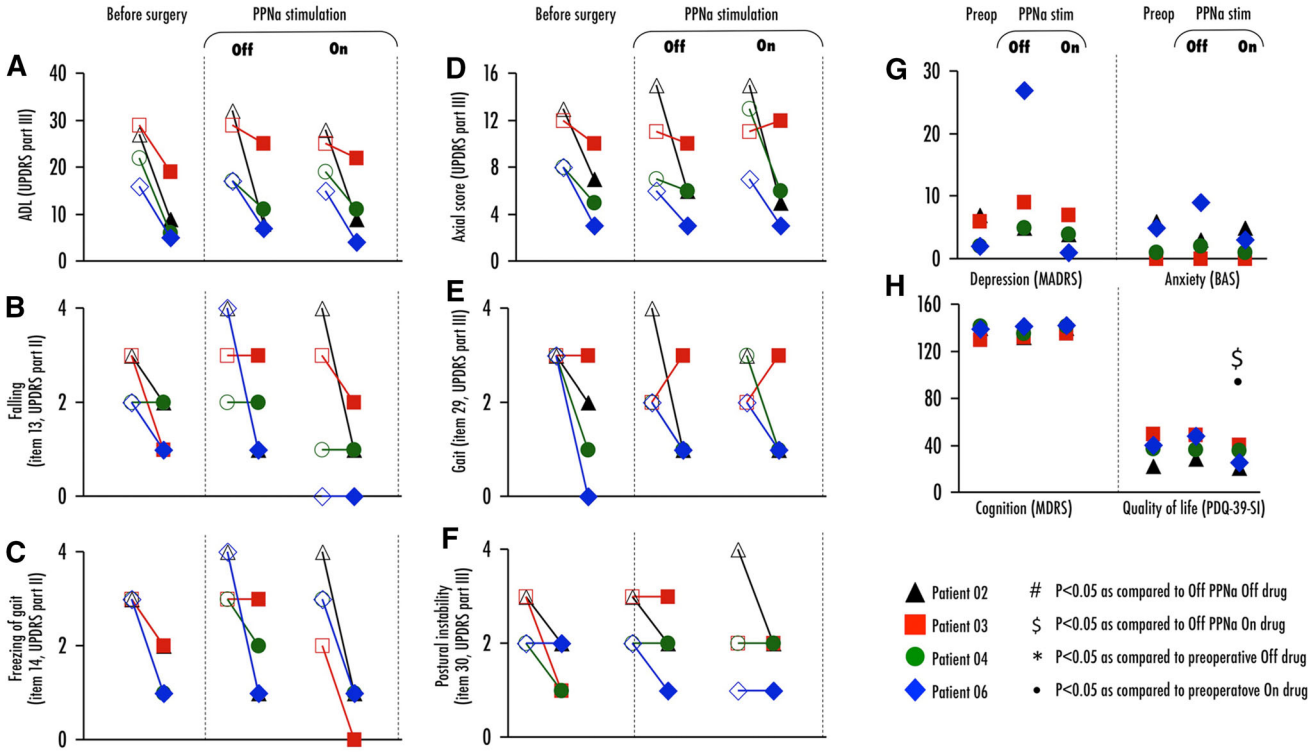


Fig. 3 Effects of PPNa-DBS on Unified Parkinson's Disease Rating Scale (UPDRS), mood, cognition and quality of life in four PD patients. Change in the activities of daily living score (ADL-UPDRS part II, **a**), falls frequency and freezing of gait subscores (items 13 and 14-UPDRS part II, **b**, **c**), axial motor signs (UPDRS part III, **d**–**f**), depression and anxiety (MADRS and BAS, **g**), cognition (MDRS, **h**), and quality of life (Parkinson's disease questionnaire-Summary Index: PDQ-39-SI, **h**), with/without PPN-DBS and with/without levodopa treatment. *Each symbol* represents one patient, without (*unfilled*) or with (*filled*) levodopa treatment

Levodopa-related complications and levodopa-equivalent dosage were not significantly modified by PPNa-DBS (mean UPDRS part IV 7.0 ± 3.2 vs 7.0 ± 3.6; mean antiparkinsonian treatment daily dosage 1138 ± 392 vs 983 ± 306 mg/day, in Off and On PPNa stimulation conditions, respectively). However, the dosages for patients 3 and 6 were reduced by 170 mg/day and 450 mg/day, respectively, after surgery.

Discussion

This study reports for the first time the effects of bilateral low-frequency PPNa-DBS on clinical and neurophysiological parameters of gait and balance in a randomised cross-over controlled study performed in six PD patients. Overall, there was no significant difference at the group level for the total RSGE score in the double-blind cross-over part of the study. However, data were only obtained for four patients because of severe adverse events.

The complex effect of PPNa-DBS

PPNa-DBS combined with levodopa treatment induced a significant improvement of FOG and a subjective decrease of the falls in three out of four patients, and was associated with a significant improvement in quality of life. Conversely, no significant effect on objective clinical gait and balance scores was detected. As previously reported, we observed a discrepancy between the magnitude of the subjective (patient interviews) and clinical objective assessments designed to evaluate the effects of PPNa-DBS [16, 17]. This suggests that the traditional objective clinical tests are unable to detect the subtle changes induced by PPNa-DBS. The interpretation of the results of our study, but also of others reports in the field, is challenged by specific difficulties to correctly assess freezing of gait and falls that are highly context dependent episodic phenomena [20], and therefore difficult to capture during experimental clinical assessment. Embedded system as proposed by others teams could allow to record gait in ecological conditions over long durations and would therefore be more

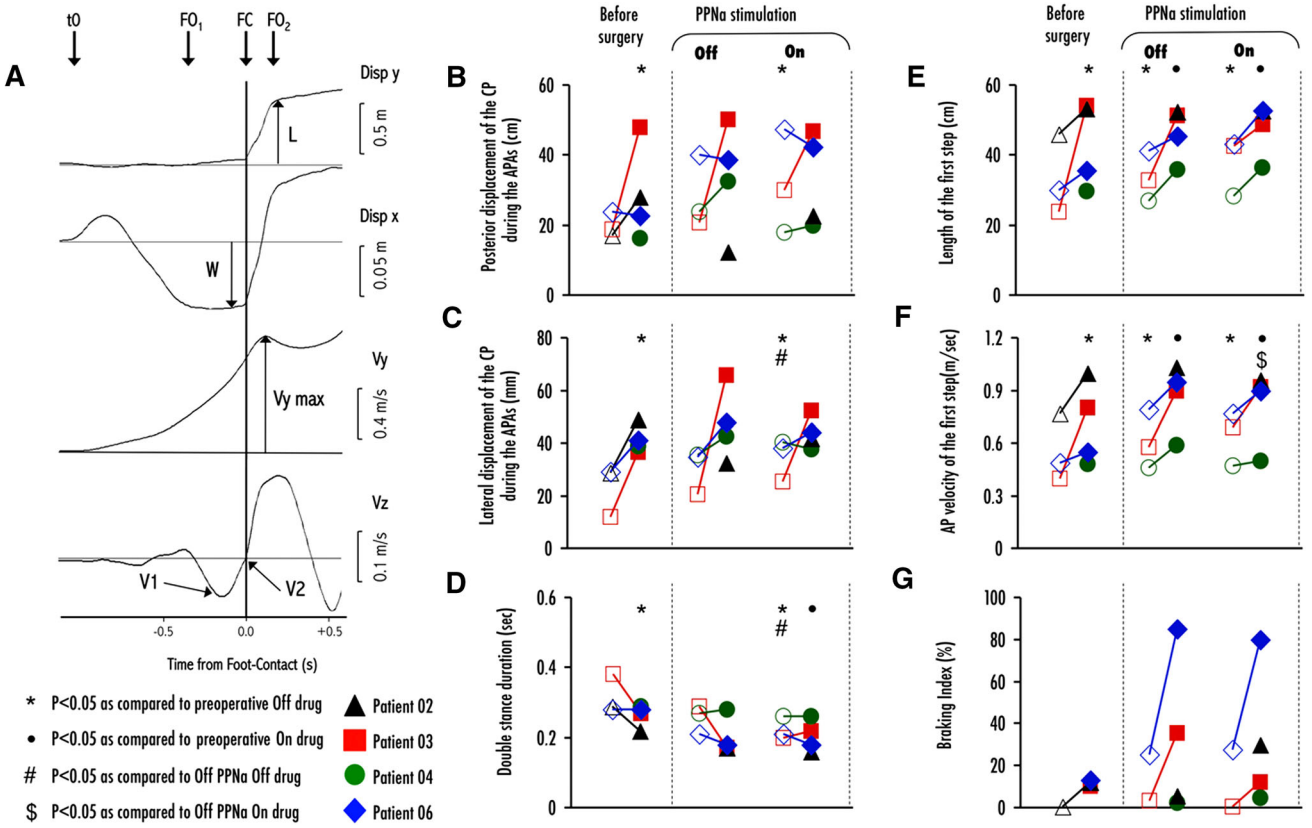


Fig. 4 Effect of levodopa treatment and PPNa-DBS on biomechanical parameters of gait initiation in four PD patients. **a** *Curves* represent from *top* to *bottom*, the anteroposterior (*Disp y*) and mediolateral (*Disp X*) CP displacements, anteroposterior CP velocity (V_y) and vertical CG velocity (V_z). The anteroposterior (y) displacement of the CP enables the measurement of the posterior displacement of the CP before the foot-off (anteroposterior APAs), the step length (L), the speed of the execution of the gait initiation ($L/t_{FC} - t_{FO1}$). The mediolateral (x) displacement of the CP enables the measurement of the lateral displacement of the CP before foot-off (mediolateral APAs) and the step width (W). With the anteroposterior velocity of the CG, the maximum forward velocity (V_y) was measured at the end of the first step. The CG vertical velocity curve enables us to measure the position of V_1 (negative peak of the CG vertical velocity) and V_2 (CG vertical velocity at the time of foot-contact) and the braking index ($((V_1 - V_2)/V_1 \times 100)$). Here, the vertical velocity of the CG describes a V shape indicating the fall in the CG (V_1). Just before foot-contact, active braking occurs and the vertical velocity increases (V_2). t_0 time of the first biomechanical event, *FO1* foot-off of the swing leg, *FC* foot-contact of the swing leg, *FO2* foot-off of the stance leg. **b–g** The *graphs* represent the effects of levodopa treatment and PPNa stimulation on the posterior (**b**) and lateral (**c**) displacement of the CP during the APAs, the double-stance duration (**d**), the length (**e**) and velocity (**f**) of the first step, and the braking capacity (**g**). *Each symbol* represents one patient, without (*unfilled*) and with (*filled*) levodopa treatment

suitable to examine the effects of PPNa-DBS in these patients [33].

Here, we used precise physiological testing to show that PPNa-DBS modifies gait initiation parameters and alleviates the postural disruption of gait initiation. We showed that these postural parameters improved with PPNa-DBS. More precisely, we showed that PPNa-DBS modified APAs and double-stance duration that are known to be related to postural instability in PD patients [34]. This result suggests that the PPN area is involved in human balance and gait initiation process. This hypothesis is in line with animal studies and clinical observations. In normal monkeys, a specific lesion of the PPN cholinergic neurons impairs posture and locomotion [5]. By modulating the PPNa in PD patients with DBS, we hypothesised that we could restore, at least partly, the cholinergic pathway to the basal ganglia, thalamus and to the descending pathways to the spinal cord [35]. Indeed, in PD patients, PPNa-DBS induces cerebral blood flow increases in the thalamus, cerebellum and midbrain region [36] and restores the H-reflex [37]. The effects of PPNa-DBS could also result from a modulation of others output or input non-cholinergic pathways via antidromic and/or orthodromic activation [38], in particular the basal-ganglia-MLR pathways, or current diffusion to structures external to PPN area, such as the cuneiform nucleus, known to control locomotion and postural controls in animals [39].

After surgery, in the absence of PPNa-DBS, length and speed of the first step (biomechanical parameters) increased but FOG and falling was aggravated in some

Table 2 Effects of bilateral PPNa-DBS on cognitive and emotional functions

	Patient 2			Patient 3			Patient 4			Patient 6		
	Before	PPNa-DBS		Before	PPNa-DBS		Before	PPNa-DBS		Before	PPNa-DBS	
		Off	On		Off	On		Off	On		Off	On
Global efficiency (MDRS, /144)	140	132	140	129	132	135	141	135	141	139	141	142
Attention [CPT-II, mean RT (s)]	476[a]	514[a]	489[a]	545[a]	567[a]	517[a]	440	454	448	344	321	391
Executive functions												
Phonological fluency (number)	18[a]	21[a]	18[a]	16[a]	18[a]	17[a]	19[a]	19[a]	24[a]	35	27	29
Trail Making test B-A (s)	ND	ND	ND	72	141[a]	87	42	36	57	26	32	33
Stroop task interference score (*T*)	51	48	50	47	47	45	50	48	53	54	62	60
CPT-II Conners—Commissions (%)	44[a]	41[a]	39[a]	19	26	25	25	59[a]	36[a]	35[a]	69[a]	44[a]
Memory												
FCRT—total free recall (/48)	25[a]	26[a]	23[a]	28	32	28	38	36	37	38	36	25[a]
FCRT—cued reactivity (%)	87	100	88	95	100	95	100	100	100	100	92	78
Rey Figure reproduction (/36)	12	14	ND	22	16	12	23	15	17	32	31	27
Visuo-spatial functions												
Rey figure copy (/36)	32	32	34	32	26	30	36	32	34	34	34	36
Visual agnosia (/12)	11	10	12	12	12	11	12	12	12	12	12	12
Facial expression recognition												
Fear (%)	50[a]	43[a]	ND	21[a]	14[a]	14[a]	43[a]	14[a]	14[a]	57[a]	64[a]	36[a]
Anger (%)	64[a]	36[a]	ND	64[a]	52[a]	52[a]	43[a]	64[a]	29[a]	79[a]	86	93
Disgust (%)	100	100	ND	79	100	100	71	86	93	86	86	79[a]
Sadness (%)	79[a]	86	ND	57[a]	71[a]	71[a]	43[a]	64[a]	29[a]	64[a]	71[a]	64[a]
Surprise (%)	100	93	ND	100	100	100	86	86	93	100	93	100
Happiness (%)	100	86	ND	100	100	100	100	100	100	100	100	100

Before surgery, Off: without PPNa stimulation after surgery, On: with PPNa stimulation after surgery

MDRS Mattis Dementia Rating Scale, *CPT* continuous performance task, *RT* reaction time

[a] Values considered below the normative values

patients. Although we did not observe significant improvement in hypokinesia (UPDRS part III) scores during the double blind period (4 months after surgery), all the patients presented an alleviation of parkinsonian symptoms shortly after surgery with increased levodopa-induced dyskinesias with their usual dosages that led to a significant reduction in dopaminergic drug treatment (with a few days' pause for one) that persisted after the end of the study in two patients. This result is in line with the concomitant improvement of hypokinesia that is visible during gait (increased length and step speed) but induction of specific dopamine-resistant gait and balance disorders after PPN lesions in parkinsonian monkeys [40]. One possible explanation could be that lesioning of the PPN area diminishes the excitatory cholinergic input to the STN [35] resulting in a decrease of its deleterious hyperactivity [41, 42]. This modification of STN activity could then lead to an alleviation of levodopa-sensitive motor parkinsonian symptoms [43], although further experiments are needed to confirm this hypothesis.

Limitations of the study and patients selection

Our study had several limitations. The main one is that the results were obtained in only four patients because of severe adverse events in two patients, that may have rendered unable to detect significant effects of PPNa-DBS. Such a limited sample was the result of a trade off between the preliminary nature of this study and our objective to demonstrate a relevant clinical effect of PPNa-DBS on gait and balance beyond the changes of biomechanical parameters.

The adverse events were those reported using the DBS technique on other targets [44]. No such side effects have been reported in patients with PPNa-DBS but the total number of patients included in these study remains very low ($n = 35$) with small samples for each study ($n = 2$–7) [13–18]. The occurrence of these surgical side-effects must be considered significant. Compared to our previous experience [45], these adverse events could indicate that these patients with advanced stages of PD are at

particularly high risk for surgical side-effects that may be not related to the structure targeted per se. To ensure the double-blind evaluation and allow the tolerability of PPNa-DBS, the stimulation parameter settings were adjusted with heterogeneous and low intensity and frequency. This could have masked a more efficient effect of PPNa-DBS, as reported with larger group of patients and/or higher intensity or frequency of stimulation [14, 17]. Moreover, the cross-over design of the study could also have influenced the results with an order effect or a carry-over effect in the absence of a wash-out period. The fact that the two patients that show the best outcome with PPNa-DBS were randomised for one in the 'Off'/'On' stimulation sequence and for the other in the 'On'/'Off' stimulation sequence suggests that this is probably not the case.

The therapeutic contacts were located bilaterally within the PPNa according to the deformable atlas that we used to target and localize postoperatively the electrodes. In comparison to previous published studies, the fact that the therapeutic contacts used in our study were located more rostrally and medially than in others published studies could explain, at least partly, the lesser improvement observed in our patients [18, 19]. Indeed, bilateral DBS applied deeper near the pontomesencephalic junction induced a significant objective improvement of the FOG with decreased duration and increased cadence during half turn in PD patients with freezing [18, 19].

Although, the overall effect on RSGE score was not significant, low-frequency PPNa-DBS could represent a treatment for the alleviation of freezing of gait and balance deficits for PD patients. However, this treatment may be more risky than other DBS surgeries in these PD patients with an advanced form of the disease. This highlights the need to carefully weigh the risks against the variable efficacy before considering PPNa-DBS as a routine option for levodopa unresponsive gait disorders. Moreover, further studies are now needed to examine which parameters of gait and postural control are more likely to be significantly improved with PPNa-DBS, the best anatomical targets and the influence of the form of the disease to accurately define an ideal target for obtaining the best therapeutic effect with PPNa-DBS. Furthermore, the performance of high-resolution analyses with functional or metabolic brain imagery could be useful for individualised predictions of the existence of dysfunction and/or a loss of cholinergic neurons of the brainstem and its relationship to the effects of PPNa-DBS.

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