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Unilateral pedunculopontine stimulation improves falls in Parkinson's disease

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Postural instability and falls are a major source of disability in patients with advanced Parkinson's disease. These problems are currently not well addressed by either pharmacotherapy nor by subthalamic nucleus deep-brain stimulation surgery. The neuroanatomical substrates of posture and gait are poorly understood but a number of important observations suggest a major role for the pedunculopontine nucleus and adjacent areas in the brainstem. We conducted a double-blinded evaluation of unilateral pedunculopontine nucleus deep-brain stimulation in a pilot study in six advanced Parkinson's disease patients with significant gait and postural abnormalities. There was no significant difference in the double-blinded on versus off stimulation Unified Parkinson's Disease Rating Scale motor scores after 3 or 12 months of continuous stimulation and no improvements in the Unified Parkinson's Disease Rating Scale part III scores compared to baseline. In contrast, patients reported a significant reduction in falls in the on and off medication states both at 3 and 12 months after pedunculopontine nucleus deep-brain stimulation as captured in the Unified Parkinson's Disease Rating Scale part II scores. Our results suggest that pedunculopontine nucleus deep-brain stimulation may be effective in preventing falls in patients with advanced Parkinson's disease but that further evaluation of this procedure is required.

Keywords: deep brain stimulation; Parkinson's disease; pedunculopontine nucleus

Abbreviations: DBS = deep-brain stimulation; OFF = off medication; ON = on medication; PPN = pedunculopontine nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Gait and postural difficulties supersede tremor, rigidity and bradykinesia as drivers of disease burden in patients with advanced Parkinson's disease (Lang and Lozano, 1998; Chapuis *et al*., 2005). Despite the importance of these problems, both medications and current surgical therapies are largely ineffective (Rodriguez-Oroz *et al*., 2005). We have been interested in understanding the pathophysiology of gait and balance disturbances in Parkinson's disease and in developing new treatments to address this large unmet need (Pahapill and Lozano, 2000; Strafella *et al*., 2008).

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Converging experimental evidence including studies in non-human primates suggests an important role for the pedunculopontine nucleus (PPN) and related brainstem areas in the control of gait and posture (Aziz *et al*., 1998; Jenkinson *et al*., 2004; Matsumura, 2005; Winn, 2006). Recent preliminary results in Parkinson's disease also suggest that PPN deep-brain stimulation (DBS) may provide benefits (Mazzone *et al*., 2005; Plaha and Gill, 2005). These studies, however, have been characterized by variable inclusion criteria and open-label evaluations. In addition, the use of multiple targets simultaneously has confounded their interpretation (Stefani *et al*., 2007). Further, there has been considerable variation and controversy on which brainstem areas have been targeted and little validation with either intra-operative physiology or postoperative structural imaging (Yelnik, 2007; Zrinzo *et al*., 2007).

To start to address these shortcomings, we now report a double-blinded evaluation of PPN DBS in six patients with intra-operative neurophysiological and postoperative imaging characterization of the surgical target. The aim of this prospective study was to investigate the safety and the effects of unilateral PPN DBS on motor signs, especially falls, freezing of gait and postural stability in patients with advanced Parkinson's disease.

Methods

Participants

From April 2006 to June 2008 we treated six patients with advanced Parkinson's disease with unilateral PPN DBS. Inclusion criteria were: (i) idiopathic Parkinson's disease; (ii) age <70 years; (iii) absence of dementia (determined by a detailed neuropsychological assessment) (Saint-Cyr and Trépanier, 2000) or major psychiatric co-morbidity (determined by a psychiatric consultation) (Voon *et al*., 2005); (iv) severe off-period gait and balance impairment and freezing with falls causing marked limitation in performing the activities of daily living, despite optimization of medical treatment; (v) absence of brain structural abnormalities interfering with surgery (determined by a brain 3 Tesla MRI); and (vi) absence of severe co-morbid medical disorders precluding surgery or adequate follow-up. The study was approved by the Toronto Western Hospital Ethics Board and the patients gave written consent to the study.

Surgical procedures

Electrode implantations (3387 Model, Medtronic, MN, USA) proceeded under local anaesthesia, after anti-Parkinson's disease medication being withheld overnight. The PPN contralateral to the most severely affected side of the body (in terms of rigidity and bradykinesia) was selected for implantation. The PPN region was targeted using 3D MRI (1.5 T) inversion recovery imaging and T_2-weighted axial sequences and the PPN coordinates were calculated as recently published (Weinberg *et al*., 2008). Neuronal spontaneous firing activity, evoked responses to voluntary and passive movements, and local field potentials were recorded simultaneously from two independently driven microelectrodes during the electrophysiological mapping to characterize the physiological attributes of the chosen target as we have described (Hutchison *et al*., 1998). Postoperative brain MRI was performed 1–2 days later to verify the electrode placement. An implantable pulse generator (Soletra, Medtronic) was implanted in the subclavicular region ipsilateral to the electrode under general anaesthesia, 3–5 days after the stereotactic procedure. In one patient, (n.4) who had metallic clips from a previous brain arteriovenous malformation repair, CT imaging was used instead of MRI.

MRI localization of pedunculopontine nucleus electrode contacts

Methods to assess the location of DBS electrode contacts have been previously described in detail (Hamani *et al*., 2008). Briefly, postoperative axial 3D inversion recovery and T_2-weighted images were transferred and merged in a neuronavigation system (Medtronic Navigation's FrameLink and StealthMerge applications). After registering the anterior commissures and posterior commissures, we established the location of (i) the tips of the electrodes, (ii) the entry point of the leads, (ii) the location of each electrode contact, and (iv) internal landmarks of the fourth ventricle, particularly the base (B) point, as assessed by Zrinzo and colleagues (2008). Point B is defined as the intersection between a line tangential to the floor of the fourth ventricle along the median sulcus and its perpendicular passing through the fastigium (Zrinzo *et al*., 2008).

Pedunculopontine nucleus deep-brain stimulation programming

The initial programming was scheduled within the first 2–3 months after surgery. Acute and chronic effects of the electrical parameter variables (amplitude, frequency and pulse width) at different electrode contacts were studied in off medications (OFF) condition (Defer *et al*., 1999).

During the acute stimulation phase, the side effects were first tested by progressively increasing the voltage, keeping the pulse width constant at 60 micros, and increasing frequency from 2, 5, 10, 20, 50, 70, 100 Hz to 130 and 185 Hz stimulation at each of the four contacts of the electrode (in monopolar stimulation). Clinical benefit was subsequently sought keeping the voltage 0.1 V below the threshold for side effects. At this stage, effects on bradykinesia, tremor, speech, gait and postural stability were assessed after 5 min of continuous stimulation.

During the chronic stimulation phase, different settings with 5, 20, 50, 70 and 130 Hz (initially with 60 micros, and later also with 90 and 120 micros), keeping the voltage just below the threshold for side effects, were assessed after 3–5 days of continuous stimulation, regardless whether these settings were beneficial during acute stimulation. Monopolar stimulation was always studied first, but bipolar stimulation was used when the threshold for side effects in monopolar stimulation was <1.0 V. Once chosen, the most effective setting (selected mainly on the basis of the best objective motor scores, and also taking into account subjective reports and the absence of adverse effects), was kept unchanged for the next 3 months. Subsequent minor adjustments in stimulation parameters were made as required between 3 and 12 months.

Clinical assessments

Part III (motor examination) of the Unified Parkinson's Disease Rating Scale (UPDRS) with a modification allowing for rating the individual items using half points (Fahn *et al*., 1987), the tapping test and the walking test (Defer *et al*., 1999) were used to assess the overall motor effects before surgery in OFF and ON medication condition and during the acute and chronic programming of PPN stimulation. The UPDRS part II (activities of daily living) scores were used for falls and freezing

measurements and the UPDRS part IV scores were used for assessing complications of therapy (specifically dyskinesia and OFF/ON duration) during the chronic phase. Adverse effects were recorded in detail.

Double-blinded motor assessments were conducted 3 and 12 months after commencement of continuous chronic stimulation (~6 and 15 months after surgery). At these times, patients were evaluated in the OFF/ON medications state after a 1 week period where the stimulation was randomly allocated to either on or off. This evaluation was repeated after a week with stimulation allocated to the other condition. Patients were studied in OFF condition after overnight medication withdrawal and after an acute levodopa challenge (ON) (Defer *et al*., 1999) using the same amount of levodopa given for the challenges before surgery. The total UPDRS, the tapping test and the walking test were used for these assessments. All the motor assessments were videotaped.

Statistical analysis

The primary outcome measures were the total scores of the UPDRS part II and part III and the subscores of the related sub items 13 (falling), 14 (freezing when walking), 29 (gait) and 30 (postural stability) before surgery and at the postoperative clinical end points of 3 and 12 months.

The secondary outcomes measures were the subscores of the UPDRS part III (contralateral rigidity, tremor and bradykinesia), the subscores of the UPDRS part IV (duration of dyskinesia and off periods), the contralateral tapping test, the walking test and the dose of dopaminergic treatment at baseline, 3 and 12 months after surgery.

The Wilcoxon signed rank test was used to analyse both primary and secondary outcomes.

Results

Clinical characteristics of the patients before surgery (baseline) are shown in Table 1. All had OFF freezing, OFF balance impairment and falls unrelated to freezing in both ON and OFF meds conditions. Four patients had ON freezing. All but one (n.4) had a good levodopa response (52.5% mean improvement in motor UPDRS) before surgery. Three patients had the electrode implanted in the right PPN and three in the left. The contacts used for chronic stimulation were located in the anterolateral tegmentum of the pontomesencephalic junction (Fig. 1). No intra-operative or immediate post-operative surgical adverse effects were observed. Patient n.2 had the electrode repositioned 4 months after the initial implant due to very low threshold of stimulation-induced paresthaesias and the lack of any motor improvement (data from the stimulation of the second electrode are presented here). Patient n.6 had unrelated coronary bypass surgery 2 months after PPN implantation surgery.

Acute pedunculopontine nucleus stimulation

The effects of acute stimulation were studied over 2 days, on average 20 days after the implant. No major changes in the motor UPDRS (particularly focused on contralateral bradykinesia and tremor, speech, gait and postural stability) were seen during the acute assessment within 5 min of changes in the stimulation parameters. Reversible and intensity- and frequency-dependent adverse effects of acute stimulation included contralateral paresthaesias in all patients, unilateral eye movements (oscillopsia) (Ferraye *et al*., 2009) in five patients and contralateral warm sensation in three patients, likely related to excitation of the medial lemniscus, oculomotor system and spinothalamic tract.

Chronic pedunculopontine nucleus stimulation

The effects of 3- to 5-day stimulation with different settings were studied in open fashion over 2 months. On average, 14 settings (range 9–25) of stimulation were assessed. Settings with frequency of 50 Hz and 70 Hz, pulse width of 60 micros and voltage of 1.9 (range 0.7–3.8) usually produced better motor scores. Bipolar stimulation elicited better motor outcomes than monopolar settings. The choice of which setting and contacts should be used for chronic stimulation was made according to the threshold for side effects (usually paresthaesias) induced by increasing voltage, the improvement in the motor UPDRS scores (even if modest) and

Table 1 Main clinical characteristics of the Parkinson's disease patients at the time of surgery

Patient No.	Sex	Age (years)	Parkinson's disease duration (years)	UPDRS-II OFF/ON	Falling (UPDRS-II item 13) off/on	Freezing (UPDRS-II item 14) off/on	Total UPDRS-III OFF/ON	Levodopa response (%)	Gait (UPDRS-III item 29) OFF/ON	Postural stability (UPDRS-III item 30) OFF/ON	LEDD (mg)
1	M	63	10	24.5/7	4/2	3/0	34.5/20	42	2.5/0.5	3/1	2100
2	M	68	15	22/10	2/2	3/1	41/21	49	2.5/0.5	2.5/1	1075
3	M	65	21	20/12	3/3	2/1	44.5/20	52	2/0.5	2/1	1800
4	F	63	11	25/13	3/3	2/2	43.5/35	20	2/1.5	2/2	300
5	M	65	25	28/15	3/1	3/3	34.5/9	71.4	2/0.5	2/0	1700
6	M	67	11	22/10	2/1	3/0	29/5.5	82	2.5/0.5	1.5/0	1435
Mean (SD)		65.2 (2.0)	15.5 (6.2)	23.6(2.8)/ 11.2(2.8)	2.8(0.7)/ 2.0(0.9)	3.0(1.0)/ 1.0(1.0)	37.8(6.1)/ 18.4(10.4)	52.5 (21.6)	2.25(0.3)/ 0.7(0.4)	2.2(0.5)/ 0.8(0.7)	1401.3 (641.4)

Scores are presented as mean (SD). LEDD = Levodopa equivalent daily dose.

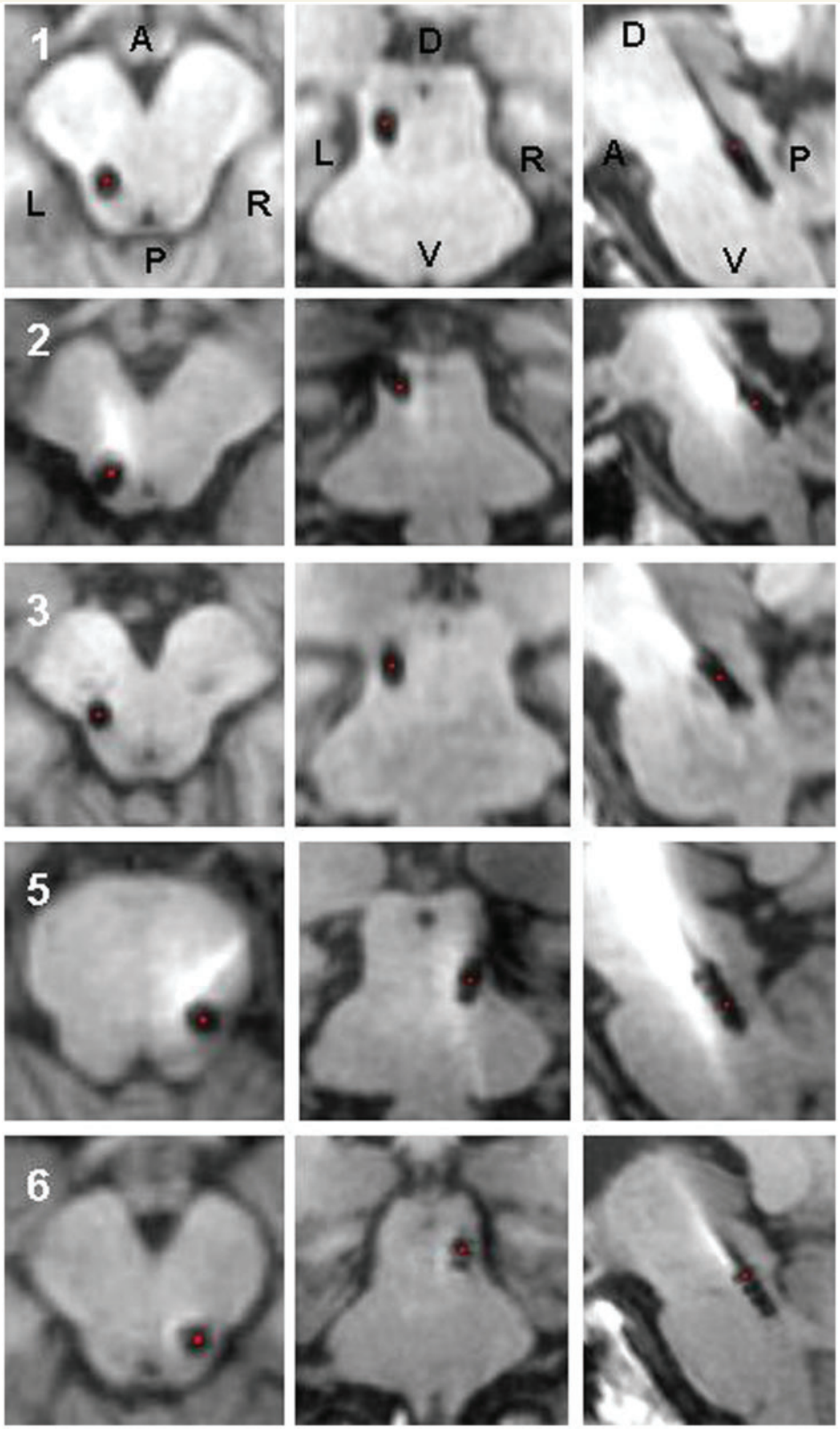

Figure 1 Location of the electrodes in patients treated with PPN DBS Axial (left), coronal (middle) and sagittal (right) MRI sections showing the placement of electrodes in our study. Red dots were placed over the centre of the contacts used as cathodes. Numbers in the left correspond to those assigned to each patient in the tables containing clinical data. A = anterior; P = posterior; L = left; R = right; D = dorsal; V = ventral. Patient 4 only had CT imaging and therefore was not included.

Table 2 Comparison between data obtained in off stimulation and on stimulation condition (and off and on medication) during the double-blind assessment in six patients after 3 and 12 months of continuous PPN stimulation

	Medication OFF						Medication ON					
	Stim off		Stim on		*P*-value		Stim off		Stim on		*P*-value	
	3 mo	12 mo	3 mo	12 mo	3 mo	12 mo	3 mo	12 mo	3 mo	12 mo	3 mo	12 mo
UPDRS-II Total	16.7 ± 3.7	21.3 ± 5.4	15.6 ± 5.9	19.9 ± 6.0	0.59	0.10	9.2 ± 3.3	9.7 ± 2.5	7.8 ± 2.8	9.5 ± 2.5	0.17	0.98
Falling (item 13)	1.3 ± 0.8	1.2 ± 1.0	1.0 ± 0.9	0.8 ± 0.9	0.56	0.31	0.8 ± 0.7	0.5 ± 0.6	0.5 ± 0.5	0.5 ± 0.5	0.17	0.98
Freezing (item 14)	2.0 ± 1.0	2.5 ± 0.5	1.0 ± 0.9	2.0 ± 1.0	0.10	0.17	1.0 ± 1.0	1.0 ± 1.0	0.7 ± 0.8	0.3 ± 0.5	0.89	0.78
UPDRS-III Total	33.8 ± 7.4	34.5 ± 4.4	32.1 ± 8.6	34.1 ± 8.5	0.58	0.91	17.9 ± 6.8	13.5 ± 17.6	19.7 ± 10.5	16.4 ± 8.0	0.71	0.46
Gait (item 29)	1.8 ± 0.7	2.0 ± 0.7	1.4 ± 0.7	2.0 ± 0.6	0.46	0.98	0.6 ± 0.5	0.9 ± 0.9	0.8 ± 0.7	0.3 ± 0.5	0.17	0.10
Balance (item 30)	1.5 ± 0.4	1.7 ± 1.0	1.2 ± 0.8	1.3 ± 1.0	0.34	0.27	1.0 ± 0.8	0.7 ± 0.8	1.2 ± 0.7	0.7 ± 0.8	0.15	0.65
Walking test time	23.25 ± 23.0	39.0 ± 34.8	14.8 ± 4.5	34.9 ± 29.1	0.50	0.83	10.8 ± 1.5	28.6 ± 43.4	11.7 ± 2.3	10.1 ± 1.4	0.31	0.14
Walking test steps	18.8 ± 13.3	21.9 ± 13.6	12.9 ± 3.9	17.4 ± 7.5	0.78	0.50	9.4 ± 1.4	9.7 ± 9.6	9.8 ± 1.5	9.1 ± 1.2	0.26	0.20
Contralateral tapping test	98.7 ± 18.6	90.3 ± 21.5	95.3 ± 17.5	90.2 ± 12.8	0.34	0.91	106.2 ± 17.1	101.0 ± 16.9	98.2 ± 12.9	106.7 ± 14.9	0.02	0.34

Scores are presented as mean (SD). Walking time is measured in seconds.

Table 3 Effects of unilateral PPN stimulation on UPDRS part II and subscores at baseline (before surgery), and after at 3 and 12 months of stimulation OFF medication

Patient no.	UPDRS-II total score				UPDRS-II item 13 (falling)				UPDRS-II item 14 (freezing when walking)			
	Preoperative	3 months	12 months	*P*-value	Preoperative	3 months	12 months	*P*-value	Preoperative	3 months	12 months	*P*-value
1	24.5	16	15		4	0	0		3	0	1	
2	22	5	27		2	0	1		3	0	3	
3	20	16	20		3	2	2		2	2	2	
4	25	15	25		3	1	2		2	1	2	
5	28	23	23		3	1	0		3	1	2	
6	22	19	13		2	2	0		3	2	2	
	23.6 (2.8)	15.6 (5.9)	19.9 (6.0)	0.02* 0.2**	2.8 (0.7)	0.9 (0.8)	0.8 (0.9)	0.04* 0.02**	3.0 (1.0)	1.0 (0.9)	2.0 (1.0)	0.04* 0.10**

Scores are presented as mean (SD). The *P*-values were calculated comparing scores at 3 and 12 months versus baseline.
*3 months versus baseline; **12 months versus baseline.

Table 4 Effects of unilateral PPN stimulation on contralateral tremor, rigidity, bradykinesia, tapping test, walking time and levodopa equivalent daily dose at baseline (before surgery), after 3 and 12 months of stimulation OFF medication

	OFF medications Preoperative	3 months	12 months	*P*-value
UPDRS-III (contralateral scores)	Six patients			
Tremor (item 20 and 21)	1.6 (0.9)	0.9 (1.2)	1.2 (1.6)	0.06*/0.46**
Rigidity (item 22)	3.1 (1.1)	2.3 (1.5)	2.2 (1.2)	0.14*/0.18**
Bradykinesia (item 23, 24, 25 and 26)	6.9 (2.7)	6.9 (2.4)	7.6 (2.4)	0.68*/0.91**
Tapping test (contralateral scores)	86.5 (17.0)	95.3 (17.5)	90.0 (12.8)	0.04*/0.22**
Walking test time	28.4 (14.7)	14.8 (4.5)	34.9 (29.1)	0.04*/0.91**
Walking test steps	21.2 (8.2)	12.9 (3.9)	17.4 (7.5)	0.09*/0.46**
LEDD	1401.3 (641.4)	1226.3 (521.2)	1158.3 (594.0)	0.17*/0.34**

Scores are presented as mean (SD). The *P*-values were calculated comparing scores at 3 and 12 months versus baseline.
*3 months versus baseline; **12 months versus baseline. Walking time is measured in seconds.

the patient's subjective opinion. No new side effects were observed during the chronic phase of stimulation.

Double-blinded assessment at 3 months

There were no statistically significant differences in the UPDRS-II or III total scores and subscores for falling and freezing or for gait and balance between on and off stimulation in ON and OFF conditions during the double-blinded assessment after 3 months of continuous stimulation (Table 2). The only score that changed significantly in the double-blind assessment of stimulation was a decrease (worsening) in contralateral finger tapping in the on-meds condition.

In contrast, in the open-label assessment, there was significant improvement in the total UPDRS-II scores (33.9%), in the OFF condition with stimulation on for 3 months compared to baseline. This reported improvement was driven predominantly by improvements in the subscores for falling (68%) and freezing (66.7%) (Table 3). Scores on the contralateral tapping test and walking time were also significantly improved ($P = 0.04$) (Table 4). Although improved, the magnitude of the benefit in the total motor UPDRS scores (15.1%), gait (36.4%) and postural stability (40.0%) subscores (Table 5) did not reach statistical significance. Contralateral tremor, rigidity and number of steps during the walking test trended towards improvement after surgery but this also did not reach statistical significance (Table 4).

In the ON condition with stimulation on, falling subscores were also significantly improved after surgery ($P = 0.04$; 75%) (Table 6). There was also a trend towards improvement in the total UPDRS-II scores (30%) and in the freezing subscores (30%), but this was not significant when compared to baseline. There was no significant difference in the total motor UPDRS scores and gait and balance subscores (Table 7). Levodopa equivalent daily dose was decreased (12.5%) but not significantly. The UPDRS-IV total scores and the subscores 32 (dyskinesia duration) and 39 (off duration) did not differ from baseline (data not shown).

No adverse events complications related to chronic stimulation were reported by the patients.

Double-blinded assessment at 12 months

Similar to what was noted after 3 months of PPN DBS, there was no significant difference in motor outcomes in the double-blinded assessments between on and off stimulation assessments (both ON and OFF medication) after 12 months of stimulation (Table 2). Further, there were no changes in total or in the tremor, rigidity, or bradykinesia subcomponent scores in the OFF state compared to baseline (Table 5).

As assessed using the UPDRS part II however, the benefits in falling observed at 3 months persisted at 12 months. Compared to baseline, falling at 12 months improved by 71% in the OFF condition and by 75% in the ON condition, levels that were similar to those seen at 3 months (Tables 3 and 7). There was a tendency for motor scores to decline from 3 to 12 months (Tables 4, 5, 6 and 7). The falling component of UPDRS II was the measure that showed less deterioration and in fact was slightly better at after 12 versus 3 months of PPN stimulation (Table 3).

Parameters of stimulation were for the most part stable from 3 to 12 months after the initiation of continuous stimulation (Table 8). No adverse events/complications related to stimulation were reported by the patients at 12 months.

Electrode position

DBS contacts used for chronic stimulation were localized in the anterolateral tegmentum of the pontomesencephalic junction (Figure). The position of the active electrode (Table 9) was consistent with the previously described position of the PPN region (Zrinzo *et al.*, 2009).

Discussion

We present the first report of unilateral PPN DBS in advanced Parkinson's disease patients assessed in a double-blinded fashion after surgery.

There were no major objective or subjective motor differences in the on versus off stimulation assessment conditions at 3 or 12 months in either the ON or OFF states. However, the most

Table 5 Effects of unilateral PPN stimulation on UPDRS part III and subscores at baseline (before surgery), after 3 and 12 months of stimulation OFF medication

Patient No.	UPDRS-III total score				UPDRS-III item 29 (gait)				UPDRS-III item 30 (postural stability)			
	Preoperative	3 months	12 months	*P*-value	Preoperative	3 months	12 months	*P*-value	Preoperative	3 months	12 months	*P*-value
1	34.5	37.5	37.5		2.5	1	1		3	0	0	
2	41	18	32		2.5	0.5	2		2.5	1.5	1.5	
3	44.5	36	25		2	2	1		2	1.5	0	
4	43.5	42	51		2	1	3		2	2	3	
5	34.5	32	33		2	2	2		2	2	2	
6	29	27	29		2.5	2	2		1.5	0.5	1	
	37.8 (6.1)	32.1 (8.6)	34.1 (8.5)	0.17* 0.5**	2.2 (0.3)	1.4 (0.7)	2.0 (0.6)	0.06* 0.36**	2.0 (0.7)	1.2 (0.8)	1.3 (1.0)	0.06* 0.17**

Scores are presented as mean (SD). The *P*-values were calculated comparing scores at 3 and 12 months versus baseline.
*3 months versus baseline; **12 months versus baseline.

Table 6 Effects of unilateral PPN stimulation on UPDRS part II and subscores at baseline (before surgery), after 3 and 12 months of stimulation ON medication

Patient No.	UPDRS-II total score				UPDRS-II item 13 (falling)				UPDRS-II item 14 (freezing when walking)			
	Preoperative	3 months	12 months	*P*-value	Preoperative	3 months	12 months	*P*-value	Preoperative	3 months	12 months	*P*-value
1	7	9	7		2	0	0		0	0	0	
2	10	4	12		2	0	1		1	0	1	
3	12	8	10		3	1	1		1	0	0	
4	13	10	13		3	1	1		2	1	1	
5	15	5	9		1	0	0		3	2	0	
6	10	11	6		1	1	0		0	1	0	
	11.2 (2.8)	7.8 (2.8)	9.5 (2.5)	0.21* 0.28**	2.0 (0.9)	0.5 (0.5)	0.5 (0.5)	0.04* 0.02**	1.0 (1.0)	0.7 (0.8)	0.3 (0.5)	0.22* 0.10**

Scores are presented as mean (SD). The *P*-values were calculated comparing scores at 3 and 12 months versus baseline.
*3 months versus baseline; **12 months versus baseline.

Table 7 Effects of unilateral PPN stimulation on UPDRS part III and subscores at baseline (before surgery), after 3 and 12 months of stimulation ON medication

Patient No.	UPDRS-III total score				UPDRS-III item 29 (gait)				UPDRS-III item 30 (postural stability)			
	Preoperative	3 months	12 months	*P*-value	Preoperative	3 months	12 months	*P*-value	Preoperative	3 months	12 months	*P*-value
1	20	18.5	21.5		0.5	1	0		1	1	0	
2	21	8	18.5		0.5	0	0.5		1	1	1	
3	20	25	19.5		0.5	1	1		1	1.5	0	
4	35	37	31.5		1.5	2	1		2	2	2	
5	9	10.5	5.5		0.5	0	0		0	2	0	
6	5.5	19.5	16.5		0.5	1	0		0	0	1	
	18.4 (10.4)	19.7 (10.5)	16.4 (8.0)	0.4* 0.6**	0.7 (0.4)	0.8 (0.7)	0.3 (0.5)	0.75* 0.22**	0.8 (0.7)	1.2 (0.7)	0.7 (0.8)	0.17* 0.59**

Scores are presented as mean (SD). The *P*-values were calculated comparing scores at 3 and 12 months versus baseline.
*3 months versus baseline; **12 months versus baseline.

Table 8 Parameters of PPN stimulation at 3 and 12 months

Patient No.	Contacts		Amplitude (Volts)		Frequency (Hertz)		Pulse width (μsec)	
	3 months	12 months	3 months	12 months	3 months	12 months	3 months	12 months
1	3– case+	3– case+	2.2	2.3	70	70	120	120
2	2– 3+	3– case+	1.6	1.5	70	70	60	120
3	2– 1+	2– 1+	2.4	2.8	70	70	60	60
4	1– 2+	1– 2+	1.0	1.0	70	70	60	60
5	1– case+	1– case+	1.3	1.4	50	70	60	60
6	3– 2+	3– 2+	3.2	3.5	50	50	60	60
Mean (SD)			1.9 (0.8)	2.0 (0.9)	63.3 (10.3)	66.7 (7.5)	70 (24.5)	70 (22.4)

Table 9 Location of contact 2 in patients treated with PPN DBS relative to the posterior commissure and point B near the fourth ventricle

Patients	Posterior commissure			Point B		
	Lateral/mm	AP/mm	Vertical/mm	Lateral/mm	AP/mm	Vertical/mm
1	7.2	–5.6	–14.4	7.2	8.6	12.6
2	7.4	–6.5	–7.9	7.4	8.9	21.7
3	8.6	–2.5	–12.0	8.6	9.1	17.6
5	8.2	–3.2	–14.2	8.2	8.6	15.1
6	8.2	–4.2	–8.6	8.2	10.7	20.6
Mean ± SD	7.9 ± 0.6	–4.4 ± 1.6	–11.4 ± 3.1	7.9 ± 0.6	9.2 ± 0.9	17.5 ± 3.8
Zrinzo *et al*. (2008)						
Caudal PPN	6.8	–4.0	–13.9	6.8	4.4	14.3
Rostral PPN	6.0	–3.0	–9.0	6.0	4.2	19.3

This contact was selected for analysis as it was the most commonly used during chronic stimulation. Patient 4 did not have a brain MRI for the reason explained in the text. In the bottom of the Table the coordinates of the rostral and caudal PPN are taken from Zrinzo et al., 2008. AP = anteroposterior.

striking result was the patients' report of significant improvement of falls both in ON and OFF condition (using the UPDRS part II) produced by unilateral PPN DBS compared to before surgery. This effect was seen at 3 months and persisted at 12 months.

Notable improvement in the subjective UPDRS-II scores (total scores and subitems for falling and freezing) was accompanied by improvements in certain objective measures including contralateral tapping and other gait parameters (walking time) at 3 months. However, at 12 months of PPN stimulation only falling (both in ON and OFF condition) was still significantly better than before surgery.

The quantitative assessment of freezing is challenging, due to its unpredictable and episodic nature, the appearance most frequently at home during unobserved behaviour, and the response to specific environmental triggers and its sometimes rare occurrence in the gait lab (Giladi and Nieuwboer, 2008; Snijders *et al*., 2008). Further, the UPDRS part II and the UPDRS part III are perhaps not the best tools to assess gait and freezing in Parkinson's disease. Being aware of these issues, we have also studied some of our unilateral PPN DBS patients using gait dynamics and static posturography. Data analysis from these assessments is in progress.

Also of importance in a study of this type with a new target for DBS, is that there were no significant permanent adverse events induced by the chronic stimulation of the PPN region at 1 year follow-up. In addition, we observed that non-motor features such as rapid-eye movement sleep (Lim *et al*., 2009) can also be improved by unilateral PPN DBS. These observations are especially relevant as we assess the possible risk to benefit ratio of surgical interventions in eloquent brain areas. However, the absence of adverse events in our small case series, and in the other PPN DBS patients reported so far, does not reduce or eliminate the risk of surgical complications observed in DBS surgery (Hamani and Lozano, 2006). It is also possible that PPN DBS can induce new adverse events, not presently captured because of the small number of patients who have undergone this surgery and lack of long-term follow-up.

We are puzzled and do not know the reason for the lack of significant differences (except for a worsening of contralateral tapping at 3 but not 12 months) between on and off stimulation scores after 3 or 12 months of continuous PPN stimulation. This may be due to a number of factors including the small sample size, lack of sensitivity of the measuring instruments used, insertion with neural disruption-related changes in function, a placebo component and a prolonged maintenance of benefit after cessation of chronic stimulation. One of the patients (n.1) had a clear benefit with insertion before stimulation was initiated. We speculate that this could be related at least in part, to an interruption of the inhibitory descending pallidal outflow to PPN- a 'pallidotomy-like' effect. Understanding how each of these various elements and mechanisms possibly contribute to the benefits we observe will require additional study. Our leading hypothesis at this time is that the benefits that outlast the cessation of stimulation relate to a prolonged washout effect, that is, a long lasting plastic change in the circuitry of posture and gait as a consequence of prolonged continuous stimulation. Consistent with this notion, we and others have observed delayed and progressive clinical benefit with stimulation and a similar prolonged washout effect lasting several weeks after discontinuation of stimulation in patients with DBS for epilepsy (Hodaie *et al*., 2002), depression (Mayberg *et al*., 2005) and dystonia (Goto *et al*., 2004).

The selection of the optimal parameters of stimulation to be used as chronic setting was challenging, since often no acute motor worsening or improvement in motor function were seen during the stimulation programming. In particular, we did not see worsening of bradykinesia using relatively high frequency of stimulation (80 Hz) as previously reported (Mazzone *et al*., 2005). Further, the stimulation frequency varies considerably from 20 to 175 Hz across various groups (Mazzone *et al*., 2005, Plaha and Gill, 2005). This indicates that the issue of the optimal frequency remains to be resolved and requires further investigation.

The results we show here support the important role of the PPN region in regulating the neural elements responsible for falls (Aziz *et al*., 1998; Pahapill and Lozano, 2000; Winn, 2006) and suggest that PPN DBS could be an important therapeutic target for advanced Parkinson's disease patients with levodopa-resistant axial signs, particularly falls. This is of interest because such patients are likely to have less favourable outcome with subthalamic nucleus or globus pallidus internus DBS (Rodriguez-Oroz *et al*., 2005). The mechanisms of action of DBS in the PPN region are probably many and are still to be determined but

they could include modulation of either ascending and/or descending projections and effects outside the motor system on sleep and alertness as we have recently documented using positron emission tomography (Strafella *et al*., 2008; Ballanger *et al*., 2009) and sleep architecture studies (Lim *et al*., 2009). Of interest, recent experimental work involving spinal stimulation in rodents suggests that that modulation of the lemniscal system may have anti-parkinsonian effects (Fuentes *et al*., 2009). Given the proximity of the PPN electrodes to the medial lemniscus and the relatively low current threshold required to produce paresthaesias, we also have to consider that some benefits PPN region stimulation may be mediated by stimulation of the lemniscal system.

In conclusion, we feel that PPN DBS merits evaluation in a larger group of Parkinson's disease patients with gait and postural disturbances who are disabled by falls.

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