Article

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FERRAYE, M U, *et al*.

Abstract

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Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease

M. U. Ferraye,[1,2] B. Debû,[1,2] V. Fraix,[1,2] L. Goetz,[1,2] C. Ardouin,[3] J. Yelnik,[4,5,6] C. Henry-Lagrange,[1,2] E. Seigneuret,[3] B. Piallat,[1,2] P. Krack,[1,2,3] J.-F. Le Bas,[1,2,3] A.-L. Benabid,[1,2,3] S. Chabardès[1,2,3] and P. Pollak[1,2,3]

1 University of Grenoble, France
2 INSERM, U836, Grenoble Institute of Neuroscience, France
3 University Hospital of Grenoble, France
4 INSERM UMR_S975, Fédération de Neurologie, Paris, France
5 University Pierre et Marie Curie, Paris, France
6 Hôpital de la Pitié-Salpêtrière, Paris, France

Correspondence to: B. Debû,
Université de Grenoble,
INSERM U836,
CHU de Grenoble,
Pavillon de Neurologie,
BP217, 38043 Grenoble Cedex 9,
France
E-mail: Bettina.Debu@ujf-grenoble.fr

Gait disturbances are frequent and disabling in advanced Parkinson's disease. These symptoms respond poorly to usual medical and surgical treatments but were reported to be improved by stimulation of the pedunculopontine nucleus. We studied the effects of stimulating the pedunculopontine nucleus area in six patients with severe freezing of gait, unresponsive to levodopa and subthalamic nucleus stimulation. Electrodes were implanted bilaterally in the pedunculopontine nucleus area. Electrode placement was checked by postoperative magnetic resonance imaging. The primary outcome measures were a composite gait score, freezing of gait questionnaire score and duration of freezing episodes occurring during a walking protocol at baseline and one-year follow-up. A double-blind cross-over study was carried out from months 4 to 6 after surgery with or without pedunculopontine nucleus area stimulation. At one-year follow-up, the duration of freezing episodes under off-drug condition improved, as well as falls related to freezing. The other primary outcome measures did not significantly change, nor did the results during the double-blind evaluation. Individual results showed major improvement of all gait measures in one patient, moderate improvement of some tests in four patients and global worsening in one patient. Stimulation frequency ranged between 15 and 25 Hz. Oscillopsia and limb myoclonus could hinder voltage increase. No serious adverse events occurred. Although freezing of gait can be improved by low-frequency electrical stimulation of the pedunculopontine nucleus area in some patients with Parkinson's disease our overall results are disappointing compared to the high levels of expectation raised by previous open label studies. Further controlled studies are needed to determine whether optimization of patient selection, targeting and setting of stimulation parameters might improve the outcome to a point that could transform this experimental approach to a treatment with a reasonable risk–benefit ratio.

Abbreviations: PPNa = pedunculopontine nucleus area; STN = subthalamic nucleus; UPDRS = Unified Parkinson Disease Rating Scale

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Introduction

Gait disorders are common in the elderly people and in patients with Parkinson's disease. Both populations are prone to falls, with severe consequences on independence and quality of life. Understanding the mechanisms underlying gait disorders is therefore a major public health priority. Falls can result from postural instability and/or freezing of gait (Bloem *et al*., 2004), a disabling symptom defined as a general inability to produce effective steps, whether at initiation or in the course of walking. In advanced Parkinson's disease, gait disorders and freezing respond poorly to levodopa and subthalamic nucleus (STN) stimulation (Krack *et al*., 2003). Animal studies have shown the involvement of the pedunculopontine nucleus area (PPNa) in the control of locomotion (Garcia-Rill *et al*., 1987; Munro-Davies *et al*., 1999; Pahapill and Lozano, 2000; Nandi *et al*., 2002; Takakusaki *et al*., 2003; Jenkinson *et al*., 2009). In humans, clinical and pathological observations (Hirsch *et al*., 1987; Jellinger, 1988; Zweig *et al*., 1989; Kuo *et al*., 2008) and reports of dramatic improvement of gait disorders following pedunculopontine nucleus stimulation support this idea (Mazzone *et al*., 2005; Plaha and Gill, 2005; Stefani *et al*., 2007). We have undertaken a prospective study of the effects of PPNa stimulation in patients with Parkinson's disease who progressively developed severe gait disorders and freezing despite optimal dopaminergic drug treatment and STN stimulation efficient on the triad symptoms.

Methods

Patients

We recruited six patients with Parkinson's disease and severe gait disorders and freezing despite STN stimulation [off levodopa, 52% median improvement on the motor part of the Unified Parkinson Disease Rating Scale (UPDRS; Fahn and Elton, 1987) on versus off stimulation, at the time of PPNa surgery]. Table 1 describes the patients' clinical characteristics and pharmacological treatments (Deuschl *et al*., 2006). Patients were included if gait disorders and freezing were the main complaints. Exclusion criteria included surgical contraindications and cognitive impairment (score below 130 on the Mattis dementia rating scale). The study was conducted at the Grenoble University Hospital in accordance with the Declaration of Helsinki and was approved by the local ethics committee. All patients provided written informed consent.

Study design

The study lasted for 1 year (Fig. 1). Patients were assessed during the month preceding surgery (baseline). After 3 months of open setting of the stimulation parameters, a double-blind cross-over study was conducted during months 4–6 after surgery. A final assessment took place 1 year after surgery.

Assessments

Assessment included four treatment conditions before surgery (off levodopa/off STN stimulation, off levodopa/on STN stimulation, on levodopa/off STN stimulation and on levodopa/on STN stimulation), and eight at one-year follow-up (same conditions as baseline, both off and on PPNa stimulation). Assessments were carried out after overnight fasting and withdrawal of medication, and then after administration of 120% of the pre-surgery usual morning levodopa dose. At 1 year, assessments off and on PPNa stimulation were conducted on two consecutive mornings after an overnight arrest of stimulation. Stimulation was turned on at least 1 h before the assessment. The order of stimulation conditions was counterbalanced across patients.

At one-year follow-up, assessment included the complete UPDRS, the Giladi questionnaire of freezing (Giladi *et al*., 2000), Mattis Dementia Rating Scale for global cognitive assessment, a composite score for frontal-lobe dysfunction, the Beck Depression Inventory, Starkstein apathy scale and the Parkinson's disease questionnaire (PDQ-39) for quality of life (Table 2). A composite gait score was computed as the sum of items 14 and 15 ('Freezing' and 'Gait') of part II (Activities of Daily Living), and items 29 and 30 ('Postural Stability' and 'Gait') of part III (motor score), of the UPDRS. Freezing of gait was quantitatively assessed as the summed duration of the freezing episodes occurring during a walking protocol (thereafter labelled 'objective freezing'). Subjects were instructed to walk along an 8 m walkway at their normal pace, both unperturbed (three trials) and under freezing-provoking circumstances including half and full turns, obstacles along the walkway, carrying a tray or

Table 1 Clinical and demographic characteristics of the patients at the time of inclusion

	1	2	3	4	5	6	Mean ± SD
Sex	M	F	M	M	F	M	
Age at PD diagnosis	55	50	49	44	31	27	42.7 ± 11.2
Age at STN surgery	64	64	65	53	53	47	57.7 ± 7.6
Age at PPNa surgery	68	68	72	57	59	56	63.3 ± 6.8
Disease duration	13	18	23	13	28	29	20.7 ± 7.1
Levodopa equivalent daily dose (mg) (Lozano *et al*., 1995)	1025	550	800	1170	400	0	675
Improvement in the UPDRS motor score under levodopa off STN stimulation (%)	55	23	23	44	46	No levodopa treatment	
FOG (off med)	Yes	Yes	Yes	Yes	Yes	Yes	
Postural instability (off med)	Yes	Yes	Yes	no	Yes	no	

Postural instability was defined as a score ⩾2 (absence of postural response, would fall if not caught by examiner) on item 30 of the UPRDS motor score.
PD = Parkinson disease; STN = subthalamic nucleus; PPNa = pedunculopontine nucleus area; UPDRS = Unified Parkinson Disease Rating Scale; med = medication; FOG = freezing of gait.

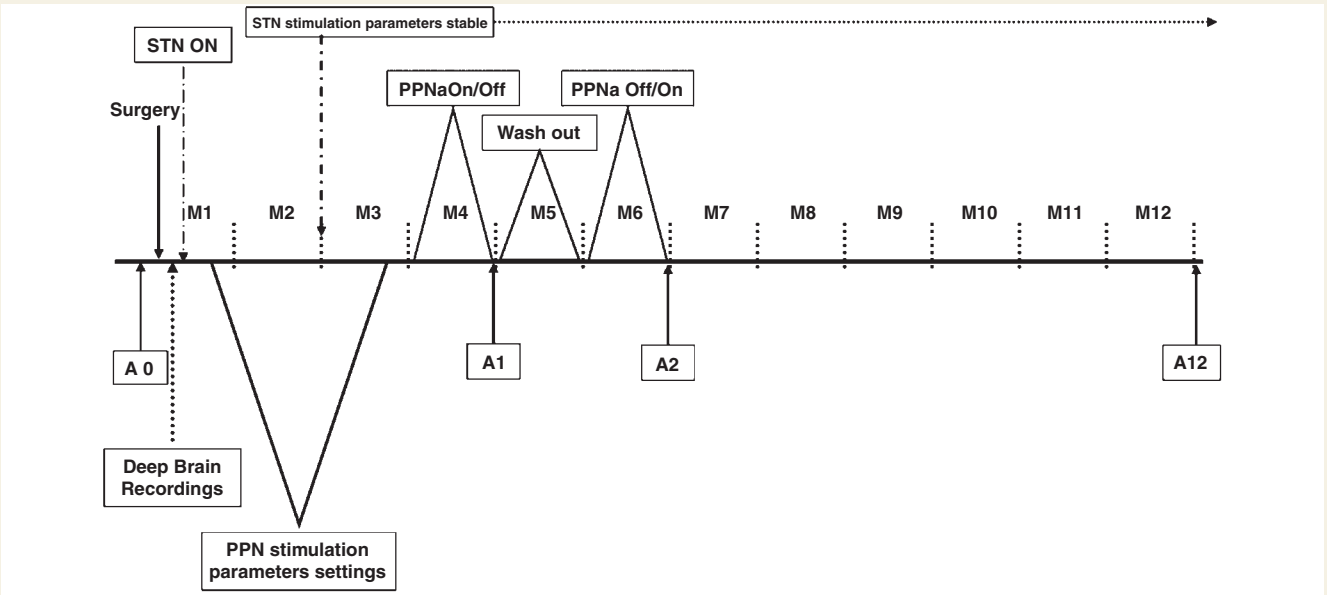

Figure 1 Study protocol.

executing a cognitive task. They also walked laterally and backwards over 4 m and walked on the spot for 30 s (two trials). These 11 trials were randomly administered. Inner soles (Stride Analyzer, B&L Engineering, Santa Ana, CA, USA) containing four footswitches (one each for the heel, big toe, first and fifth metatarsal heads), were placed in the patients' shoes. The foot–floor contact data were collected using a telemetric acquisition system (Noraxon Telemyo 2400, Scottsdale, USA) with video recording synchronization.

Assessment during the double-blind study included the motor score of the UPDRS and the walking protocol.

Surgery procedure

The PPNa was targeted bilaterally by means of stereotactic brain magnetic resonance imaging (MRI) and contrast ventriculography to define the bicommissural line and the fourth ventricle (Piallat *et al*., 2009). The average coordinates of the surgical targeting were 1.5 mm posterior to the posterior commissure, 13 mm below the bicommissural line and 6 mm lateral from the midline. The direction of the trajectory was parallel to the floor of the fourth ventricle. The trajectory was adapted to vessel constraints and to the width of the mesencephalon.

The location of all contacts was checked using the final intra-operative teleradiography (Pixray, Bioscan system, Switzerland) fused with the preoperative stereotactic MRI using image navigation software (Osirix, http://www.osirix-viewer.com/), and atlas-based neuroimaging (Yelnik *et al*., 2007; Bardinet *et al*., 2009) (Table 3 and Fig. 2). Preoperative MRIs were performed after surgically disconnecting the neurostimulator connected to the STNs in the first three patients. However, the worsening in parkinsonism was so severe, especially in Patient 3, that disconnection was not done for the remaining three patients. Intra-operative microrecordings and microstimulation were performed along two or three micro-electrode trajectories. We used two or three microelectrodes, depending on the shape of the mesencephalon of each patient, cautiously staying 3–4 mm away from the edge of the brainstem to avoid injuring blood vessels. Microrecordings were generally moderately informative because of the paucity of cells that could be recorded long enough to enable *post hoc* analyses. However, spontaneous neuronal activity, mainly fibres characterized by a first positive depolarization (Kobayashi *et al*., 2002) was helpful to delineate the margin of the medial lemniscus. We also recorded responses to passive movements and active gait mimicking. Passive movements did not evoke much change in neuronal activity. Mimicking walking and running did increase the firing rate without altering the firing pattern in two patients. Detailed data have been published elsewhere (Piallat *et al*., 2009). Stimulation at low frequency (25 Hz) induced ipsilateral oscillopsia and bilateral limb myoclonus when electrical amplitude was increased. Stimulation at 130 Hz induced paraesthesia in the contralateral hemibody. In addition, one patient reported a pleasant sensation of heat. The quadripolar electrode (model 3389 DBS, Medtronic, Minneapolis, MN, USA) was implanted along the trajectory with the greatest threshold for stimulation-induced side effects and in which cells were recorded.

Settings

Each contact was tested separately after surgery over frequencies ranging from 5 to 130 Hz and 60 μs pulse width. Side effects were examined with progressive voltage increase. Therapeutic contacts were selected based either on the absence of side effects and best clinical effect on gait assessed after a few hours or, in the absence of acute improvement, on intra-operative electrophysiological results and anatomical considerations. Setting was adjusted as required during the first three months following surgery, and the best parameters identified at 3 months were used for the double-blind study, after which adjustments of PPNa stimulation were resumed.

Data analysis

Since we focused on the effects of PPNa stimulation with STN stimulation kept unchanged as far as possible, data off STN stimulation are not shown. The primary outcome measures were the composite gait

Table 2 Individual scores on the clinical evaluations before surgery and 1 year after surgery

	1	2	3	4	5	6	Median
UPDRS II (maximal score, 52)							
Before surgery							
Off med.	16	32	25	20	14	21	20.5
On med.	14	21	18	6	14		16
After surgery							
Off med	12	27	22	16	14	17	16.5
On med	11	26	20	8	13		13.0
UPDRS III (maximal score, 108)							
Before surgery							
Off med.	21	57	19	16	18	18	18.5
On med.	23	47	30	12	18		20.5
One-year follow-up							
Off med/Off PPN	10	38	32	9	16	25	20.5
On med/Off PPN	12	31	32	4	13		19.0
Off med/On PPN	12	41	28	11	11	24	18.0
On med/On PPN	13	34	30	8	10		18.5
Mattis							
Before surgery	141	128	139	138	136	138	138
One-year follow-up	140	118	134	142	128	142	137
Frontal score							
Before surgery	46	21	35.75	43	31.3	43.6	39.4
One-year follow-up	40	17	31	35.7	37.7	47.8	36.7
Beck							
Before surgery	17	36	5	4	17	24	17
One-year follow-up	29	27	12	10	11	17	14.5
Apathy							
Before surgery	12	29	5	5	13	24	12.5
One-year follow-up	16	24	9	10	11	13	12
PDQ-39 (%)							
Before surgery	28.5	64	33	31	31	47	32
One-year follow-up	36	64	32	30	28	35	33
PDQ-39 Mobility (%)							
Before surgery	45	93	98	23	83	90	86
One-year follow-up	32	85	78	35	53	73	63

A reduction in scores indicates an improvement in function. On-medication evaluations were performed during periods of maximal effect after administration of levodopa while subthalamic nucleus stimulation was on (Krack *et al*., 2003; Deuschl *et al*., 2006).
On the Mattis Dementia Rating Scale (maximal score, 144) and the frontal-lobe test (maximal score, 50), a higher score indicates better function. On the Beck Depression Inventory (maximal score, 63) and the Starkstein Apathy Scale (maximal score, 42), a higher score indicates more severe depression and apathy, respectively. Scores for the PDQ-39 and its Mobility subscale can range from 0 to 100%, with higher scores indicating worse function.

score, the Giladi questionnaire score and the data from the walking protocol at baseline and at one-year follow-up. Secondary outcome measures included scores on parts II and III of the UPDRS, and the results of the neuropsychological tests. The double-blind study was designed to test treatment (stimulation on versus off) effects. Based on published results (Plaha and Gill, 2005; Stefani *et al*., 2007), the study was designed to have an overall power of 95% and to detect a 70% improvement, allowing 30% of variability in the composite gait score (two-tailed type I error of 5%). A change less than two points in the composite gait score (maximum 16) was considered not clinically relevant. Wilcoxon tests for paired samples were performed on all data.

Data from the walking protocol were analysed off-line. The beginning and end of each freezing episode were marked on the foot-contact data before the files were exported and further processed under Matlab (Mathworks, Inc., Natick, MA, USA) to quantify the duration of freezing during the walking test, relative to the total walking duration.

Results

All patients completed the study protocol. Patient 6 had stopped taking levodopa several years before surgery and was only evaluated off levodopa. Patient 3 greatly suffered from the arrest of STN stimulation at the time of surgery and could no longer sustain it afterwards. Indeed, at one-year follow-up, STN stimulation arrest caused him severe akinesia, breathing difficulties and gait was impossible for several days afterwards, resulting in missing data. In four patients, worsening of leg or orofacial dyskinesias required mild decrease in levodopa dose or STN stimulation parameters.

One-year follow-up

Individual data are shown in Table 4 as well as in Figs 3 and 4. All measures improved in Patient 1 whether on or off PPNa

stimulation, while they slightly worsened in Patient 2. In Patient 3, objective freezing improved both off and on levodopa, but there was no change in the composite gait score or the Giladi questionnaire score. In Patients 4 and 5, objective freezing greatly improved off medication, whether on or off PPNa stimulation, as did the Giladi questionnaire in Patient 5 and the composite gait score in Patient 4. In Patient 6, objective freezing and the Giladi questionnaire score improved, both on and off PPNa stimulation, while the composite gait score did not change.

Table 3 Coordinates of the tip of the distal contacts of the electrodes (labelled 0 on one side and 4 on the other side) implanted in the pedunculopontine area of the six patients

	Contact	Laterality X (mm)	Pontomesencephalic line	
			Antero-posterior *d* (mm)	Depth (rostro-caudal) *h* (mm)
Patient 1	0	5.35	8.7	1.5
	4	6.05	8.7	1.5
Patient 2	0	6.7	9.5	0.8
	4	7.5	9.5	0.8
Patient 3	0	5.7	7.7	−1.3
	4	5.5	7.7	−1.3
Patient 4	0	2.6	6.5	−2.9
	4	5.0	6.1	−2.9
Patient 5	0	4.7	8.9	−1.7
	4	5.4	8.4	−1.7
Patient 6	0	4.5	9.8	−1.1
	4	4.9	9.8	−1.1

Laterality is measured relative to the midline; *d*: distance (in mm) anterior to the line extending from the floor of the 4th ventricle; *h*: distance (in mm) to the pontomesencephalic line defined as the line joining the pontomesencephalic junction and the caudal quadrigeminal plate end measured on the midline (−: below this line; +: above this line).

As can been seen in Table 4, only item 14 of the UPDRS part II (freezing) showed clear improvement 1 year after PPNa implantation. Out of five patients off medication and two on medication, who scored 3 (frequent freezing; occasionally falls from freezing) or 4 (frequent falls from freezing) before surgery, only one still had falls related to freezing 1 year after surgery. Scores of the gait or postural stability items did not show consistent improvement except in Patient 1. Finally, falls unrelated to freezing were unchanged except for Patient 6 who improved.

Regarding the whole group, objective freezing off levodopa significantly improved on stimulation ($P = 0.046$) and not off stimulation ($P = 0.08$). On levodopa, there was no significant change compared to pre-surgery, whether off or on PPNa stimulation. The scores of the Giladi questionnaire, of the motor part of the UPDRS, and the composite gait score did not change significantly, whether off or on levodopa. In contrast, activities of daily living improved off levodopa ($P = 0.043$). There was no significant difference in quality of life, Mattis dementia rating scale, frontal score, Beck depression inventory and Starkstein apathy scale (Table 2).

Double-blind study

Data are presented in Fig. 5. Overall, whether off or on levodopa, there was no significant difference between the off and on

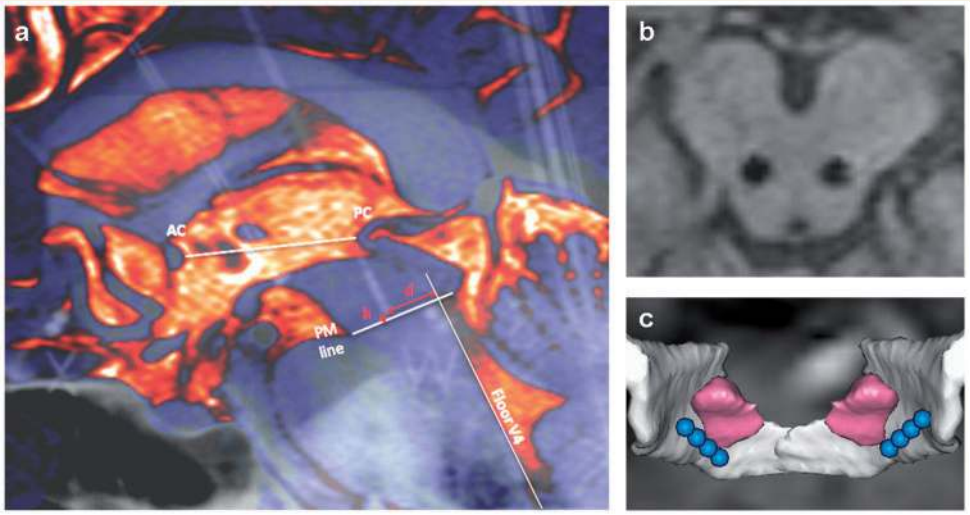

Figure 2 Location of the electrodes in the pedunculopontine area for Patient 1. (**a**) Sagittal fusion imaging of the final intra-operative teleradiography with the preoperative MRI, showing how the coordinates of the tip of the distal contacts of the electrodes were measured. h: distance (in mm) to the pontomesencephalic (PM) line, defined as the line connecting in the anterior-posterior direction the pontomesencephalic junction to the caudal end of the quadrigeminal plate, measured on the midline; AC: anterior commissure; PC: posterior commissure. d: orthogonal distance in mm to the line prolonging the fourth ventricle line. V4: fourth ventricle. (**b**) 3D T_1-weighted magnetic resonance imaging in the axial plane parallel to the bicommissural plane, at the level of contacts 1 and 5 of the electrodes. Those contacts delivered cathodic current and the contact depth of the right and left electrodes was symmetrical. (**c**) Atlas adaptation onto patient's MRI (Yelnik et al., 2007). Superior posterior view of the 3D image with the pedunculopontine nucleus in pink, the medial lemniscus in white and the four electrode contacts in blue. Note that in this patient the electrode is located posterior to the pedunculopontine nucleus.

Table 4 Individual scores for falls (item 13 of UPDRS II), freezing (item 14 of UPDRS II), gait (item 15 of UPDRS II and 30 of UPDRS III) and postural stability (item 29 of UPDRS III) both off and on medication, before and one year after surgery

Item	Medication condition		Patients						Median
			1	2	3	4	5	6	
Falls (UPDRS II)	Off	Pre-surgery	0	4	1	0	1	2	1
		Post-surgery	0	4	1	0	1	0	0.5
	On	Pre-surgery	0	4	0	0	1	–	0
		Post-surgery	0	4	1	0	1	–	1
Freezing (UPDRS II)	Off	Pre-surgery	4	3	3	3	1	3	3
		Post-surgery	1	4	2	2	1	2	2
	On	Pre-surgery	4	3	2	0	1	–	2
		Post-surgery	1	4	2	1	0	–	1
Gait (UPDRS II)	Off	Pre-surgery	2	3	3	3	3	3	3
		Post-surgery	0	3	3	1	3	2	2.5
	On	Pre-surgery	2	3	3	0	3	–	3
		Post-surgery	0	3	3	1	3	–	3
Gait (UPDRS III)	Off	Pre-surgery	1	3	2	1	2	2	2
		Post-surgery	0	3	4	0	2	2	2
	On	Pre-surgery	1	1	2	0	2	–	1
		Post-surgery	0	2	2	0	1	–	1
Postural Stability (UPDRS III)	Off	Pre-surgery	2	2	2	1	2	0	2
		Post-surgery	1	2	2	1	2	1	1.5
	On	Pre-surgery	2	1	2	0	0	–	1
		Post-surgery	1	1	2	0	2	–	1

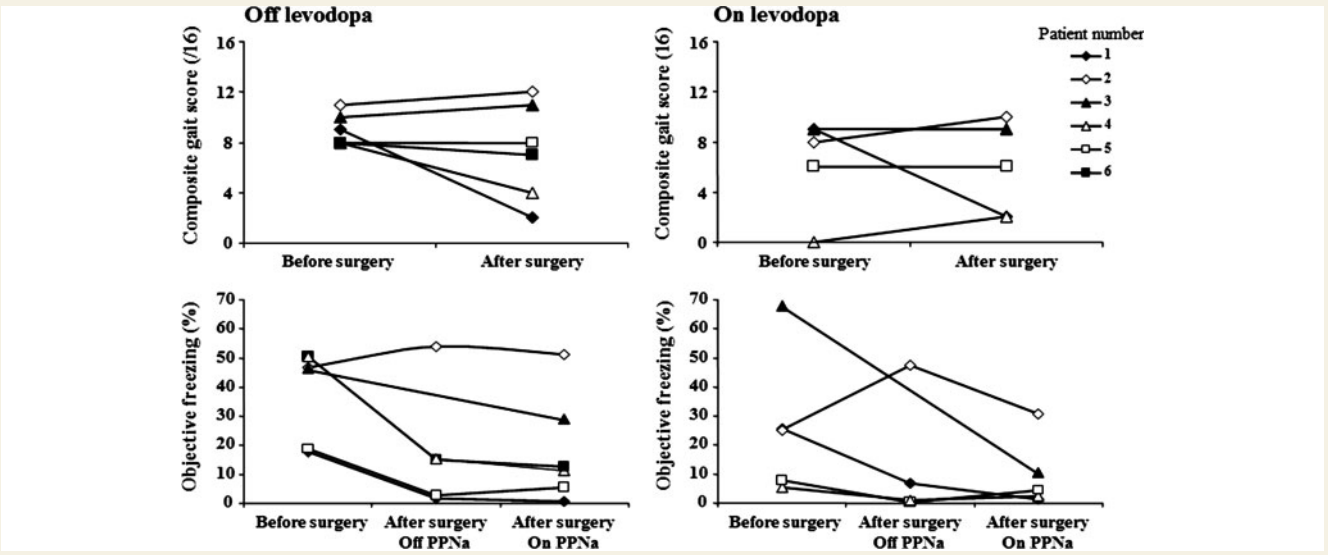

Figure 3 Composite gait score and objective freezing recorded during the walking tests before surgery and at one-year follow-up.

stimulation periods regarding objective freezing and the score on the motor part of the UPDRS. However, on levodopa, objective freezing decreased under stimulation in Patients 1 (6.2% versus 18.9%) and 3 (26.8% versus 41.1%).

Electrical parameters

Bipolar configuration was preferred when the threshold of stimulation-induced side effects was below 1.0 V using monopolar configuration. Bipolar stimulation was used for 10 of the 12 electrodes. Stimulation frequency ranged from 15 to 25 Hz, voltage was between 1.2 and 3.8 V, pulse width being set to 60 μs for 10 electrodes and to 90 μs for the two others. In all patients, many different settings were tried for periods of at least two weeks, with changes in both contacts and electrical parameters. Stimulation was set so as to be continuous for all patients during the double-blind study. We then observed a trend for the benefit to wear off. Therefore, cyclic stimulation with continuous daily

stimulation and night arrests was preferred thereafter for all but one patient, using a therapy self-controller (Access 7436, Medtronic). Patient management was further complicated by the absence of clear-cut acute beneficial effects at stimulation onset, and carryover effects at stimulation arrest. A total of 24 out-patients unplanned visits were necessary after the initial 3 months setting phase in addition to the visits planned in the protocol.

Adverse events

No serious adverse events occurred. At the time of surgery, Patient 3 had great difficulty recovering from STN stimulation arrest because of parkinsonism worsening. Patient 4 displayed two epileptic seizures 1 week after electrode implantation. These patients fully recovered from these adverse effects.

Low-frequency stimulation (5–35 Hz) induced ipsilateral oscillopsia (Ferraye *et al*., 2009). Increasing stimulation frequency over 60 Hz induced contralateral paraesthesias on 10 electrodes. Both positive and negative myoclonus of the limbs could be elicited at low frequency (nine electrodes). All of these side effects were fully reversible by reducing voltage. Chronic stimulation voltage was set 15% below the threshold of the first side effect. Three patients spontaneously reported improvement of nocturnal sleep along with an increase in diurnal vigilance.

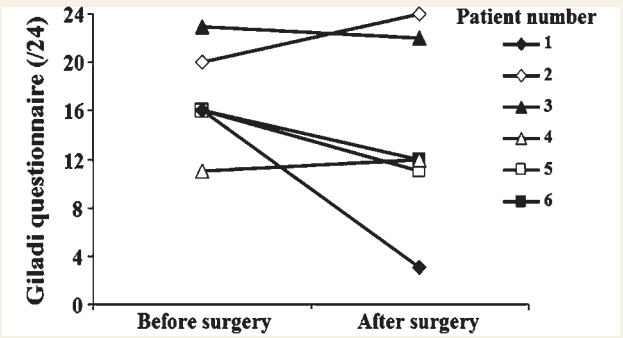

Figure 4 Scores on the Giladi questionnaire of freezing of gait before surgery and at one-year follow-up.

Electrode placement

Table 3 shows the localization of the electrodes within the PPNa. According to Yelnik's atlas (Yelnik *et al*., 2007; Bardinet *et al*., 2009), 10 of the active contacts were located in the pedunculopontine nucleus (Patients 2, 3, 5 and 6), 6 were in or close to the cuneiform and subcuneiform nuclei (Patients 1, 3 and 4), and 2 contacts were close to the medial lemniscus (Patients 2 and 5). The best effects were seen in the patients with active contacts located slightly posterior to the pedunculopontine nucleus, in the cuneiform and subcuneiform nuclei according to Olszewski and Baxter's atlas (Olszewski and Baxter, 1982).

Discussion

There has been growing enthusiasm for pedunculopontine nucleus stimulation after the encouraging reports of the first, open and short-term studies (Mazzone *et al*., 2005; Plaha and Gill, 2005; Stefani *et al*., 2007). However, the efficacy of this new target in alleviating gait disorders has yet to be objectively demonstrated. This is the first study on PPNa stimulation effects that combines clinical gait data with objective quantifications of freezing duration using a double-blind crossover design and at one-year follow-up. Our patients had undergone STN implantation 4–9 years before and had reached the well described advanced stage of Parkinson's disease where refractory gait disorders predominate (Giladi *et al*., 2001). It has been suggested that STN stimulation could lead to gait worsening in some patients (Tagliati, 2008; van Nuenen *et al*., 2008), and possibly induces plastic deleterious changes affecting locomotion in the long term (Moreau *et al*., 2008). However, we reasoned that if pedunculopontine nucleus stimulation held promises regarding gait disorders, it would be best demonstrated on these very severe cases despite the possible confounding effects of STN stimulation. Moreover, in our patients, not only did gait impairments develop years after STN stimulation, but its arrest worsened parkinsonism and gait.

The PPNa can be safely implanted (Mazzone *et al*., 2005; Plaha and Gill, 2005; Stefani *et al*., 2007). Nevertheless, the risk of bleeding, inherent to stereotactic electrode implantation, can potentially have vital consequence especially in the brainstem. Unilateral stimulation might be an alternative since the

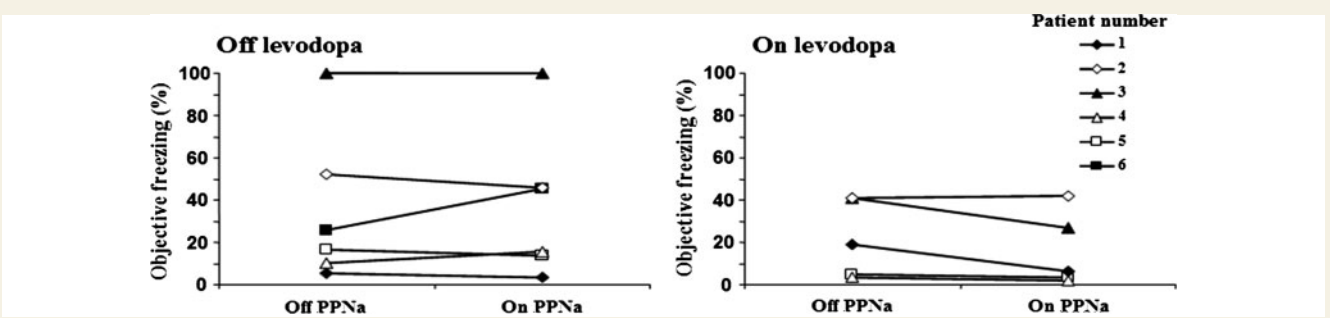

Figure 5 Objective freezing of gait measured during the walking tests during the double blind study. Patient 3 was unable to walk off levodopa because of long duration worsening in akinesia after subthalamic nucleus stimulation arrest.

pedunculopontine nuclei have bilateral connections. One year after surgery, low-frequency stimulation of this area shows variable results, from fair improvement to worsening of freezing in one case. The double-blind assessment did not show significant changes. However, our group of six patients was clearly underpowered and studying such a small sample could only detect dramatic improvement in all patients. Several factors may explain these discrepancies, including electrical stimulation setting, differences in electrode placement, or the clinical characteristics of the patients.

How to stimulate

The 24 unplanned outpatient visits stress the difficulty of patient management. This appears to be partly related to the time course of the stimulation effects. Unlike stimulation of the STN in Parkinson's disease, switching on or off PPNa stimulation did not induce acute effects. In addition, after chronic stimulation, carry-over effects lasted days, which explains the lack of differences between stimulation off or on at one-year follow-up. Together with the challenge of assessing freezing, considering its random nature and interactions with motivation and emotions, such lack of consistent acute effects of stimulation further complicated the setting of the stimulation parameters. The waning, if not total disappearance, of initial benefits, justified the remaining visits. We first interpreted this as a need to adjust the stimulation parameters. However, the loss of initial benefit was sometimes seen after a period of dramatic improvement of gait. We therefore hypothesized that development of tolerance, also reported by Stefani *et al*. (2007), could mitigate long-term benefit and turned to intermittent stimulation using overnight arrests. Tolerance has been described for thalamus stimulation in the treatment of tremor with improvements following stimulation night arrests (Dowsey-Limousin, 2002). Overall, these observations suggest that the mechanisms of action of PPNa stimulation are complex and differ from those involved in STN stimulation.

PPNa stimulation induced adverse effects at relatively low voltages, including oscillopsia and limb myoclonus at low frequency and paraesthesia at higher frequencies. The oculomotor effects are likely to result from the recruitment of the most lateral and caudal fibres of the oculomotor nerve (Ferraye *et al*., 2009). Myoclonus has been reported following low frequency stimulation of the ventral intermediate nucleus of the thalamus (Bejjani *et al*., 2000). Thus, the myoclonus following PPNa stimulation may result from the modulation of the thalamic projections. Paraesthesia occurring at stimulation frequencies above 50 Hz probably result from the lateral spreading of the current to the medial lemniscus. Consequently, we only tried frequencies between 10 and 40 Hz for periods longer than days to weeks and the final frequency setting was based on subjective evaluation. Overall, oscillopsia are the major adverse effect of pedunculopontine stimulation, as they significantly restrain the therapeutic window. Bipolar stimulation was mostly used to limit this effect.

Where to stimulate

The boundaries of the human pedunculopontine nucleus provided by atlases (Olszewski and Baxter, 1982) are poor and somewhat unreliable because it is not a nucleus *per se*, but rather a reticular structure belonging to the mesencephalic reticular formation. Hence we use the term 'pedunculopontine nucleus area', which includes the pedunculopontine nucleus and the cuneiform and subcuneiform nuclei (Olszewski and Baxter, 1982). The difficulty of delineating the pedunculopontine nucleus clearly on MRI (Zrinzo *et al*., 2008) and the use of bicommissural landmarks for indirect targeting may not be appropriate, leading to targeting inaccuracies (Mazzone *et al*., 2007; Zrinzo *et al*., 2007). Novel targeting approaches are under discussion (Mazzone *et al*., 2008; Zrinzo *et al*., 2008), taking into account the great inter-individual variability of brainstem anatomy, especially in patients with neurodegenerative disorders. Nevertheless, according to post-operative MRI and Yelnik's atlas (Yelnik *et al*., 2007; Bardinet *et al*., 2009), the distal contacts of the 12 implanted electrodes in our study are in the PPNa. In this region, the Cartesian coordinates referring to the floor of the fourth ventricle and the pontomesencephalic landmarks are more instructive than the bicommissural line. Our results could suggest that the most suitable targets are located slightly posterior to the pedunculopontine nucleus pars compacta, probably in the ventral part of the cuneiform nucleus where stimulation-induced locomotion has been reported in animals (Takakusaki *et al*., 2003). In line with MRI studies (Zrinzo *et al*., 2008), an alternative explanation of our results is that our targeting was, in average, 2 mm anterior to the pedunculopontine nucleus. In that event, the most anterior electrodes were not in the pedunculopontine nucleus pars compacta, while the most posterior electrodes were. This would explain the disappointing results in the patients with the more anterior electrodes. Further studies are needed to better correlate the Cartesian coordinates of the stimulating contacts with the clinical outcomes, and improve our knowledge of the precise area to stimulate.

Patient selection

Our criterion for patient selection was the presence of severe freezing of gait. Before surgery, in five out of the six patients, freezing occasionally or frequently led to falls. One year after surgery, only one patient still reported falls in relation to freezing. However, some patients displayed associated axial disorders, including postural instability or other symptoms interfering with gait, such as lower limb dystonia, dyskinesias or stiffness, which failed to improve under pedunculopontine stimulation. This may explain why the gait items of the UPDRS or the composite gait score did not improve although freezing *per se* decreased. These results suggest a possible functional somatotopy within the PPNa or a functional specificity regarding freezing, raising the issue of patient selection. Patients with freezing but a rather preserved gait pattern and balance between freezing episodes may be the best candidates. The lack of effect on axial symptoms, except for freezing of gait, is in contradiction with initial results reporting improvement in postural stability (Plaha and Gill, 2005; Stefani

et al., 2007). Furthermore, unlike others, we did not observe a significant, objective improvement in global motor functioning, including akinesia (Mazzone *et al*., 2005; Plaha and Gill, 2005; Stefani *et al*., 2007). This may be due to the advanced stage of parkinsonism in most patients. In keeping with some patients' subjective reports of vigilance improvement, the decrease in freezing and falls related to freezing may be related to an indirect effect of PPNa stimulation on alertness induced by activation of the reticular ascending formation.

Finally, lack of benefit as in Patient 2 may be due to the microlesion associated with electrode implantation.

Conclusions

PPNa stimulation is a sophisticated procedure for both electrode implantation and patient management. The factors predictive of its outcomes appear complex and multiple, at least in patients with previous STN stimulation. Since improvement can be fair in some patients, further evaluation in larger controlled trials is needed. Patients with severe freezing, leading to falls, may be better candidates.

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