Stereotactic and Functional Neurosurgery

Clinical Study

Stereotact Funct Neurosurg 2021;99:287–294
DOI: 10.1159/000511978

Received: June 12, 2020
Accepted: September 29, 2020
Published online: December 4, 2020

Pedunculopontine Nucleus Deep Brain Stimulation for Parkinsonian Disorders: A Case Series

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Keywords
Deep brain stimulation · Pedunculopontine nucleus · Parkinson's disease · Progressive supranuclear palsy · Freezing of gait

Abstract
Background: Deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) has been investigated for the treatment of levodopa-refractory gait dysfunction in parkinsonian disorders, with equivocal results so far. ***Objectives:*** To summarize the clinical outcomes of PPN-DBS-treated patients at our centre and elicit any patterns that may guide future research. ***Materials and Methods:*** Pre- and post-operative objective overall motor and gait subsection scores as well as patient-reported outcomes were recorded for 6 PPN-DBS-treated patients, 3 with Parkinson's disease (PD), and 3 with progressive supranuclear palsy (PSP). Electrodes were implanted unilaterally in the first 3 patients and bilaterally in the latter 3, using an MRI-guided MRI-verified technique. Stimulation was initiated at 20–30 Hz and optimized in an iterative manner. ***Results:*** Unilaterally treated patients did not demonstrate significant improvements in gait questionnaires, UPDRS-III or PSPRS scores or their respective gait subsections. This contrasted with at least an initial response in bilaterally treated patients. Diurnal cycling of stimulation in a PD patient with habituation to the initial benefit reproduced substantial improvements in freezing of gait (FOG) 3 years post-operatively. Among the PSP patients, 1 with a parkinsonian subtype had a sustained improvement in FOG while another with Richardson syndrome (PSP-RS) did not benefit. ***Conclusions:*** PPN-DBS remains an investigational treatment for levodopa-refractory FOG. This series corroborates some previously reported findings: bilateral stimulation may be more effective than unilateral stimulation; the response in PSP patients may depend on the disease subtype; and diurnal cycling of stimulation to overcome habituation merits further investigation.

Introduction

Low-frequency deep brain stimulation (DBS) of the pedunculopontine nucleus (PPN) in Parkinson's disease (PD) and atypical parkinsonian disorders has been reported to improve levodopa-refractory freezing of gait (FOG) and reduce frequency of falls in some patients [1–

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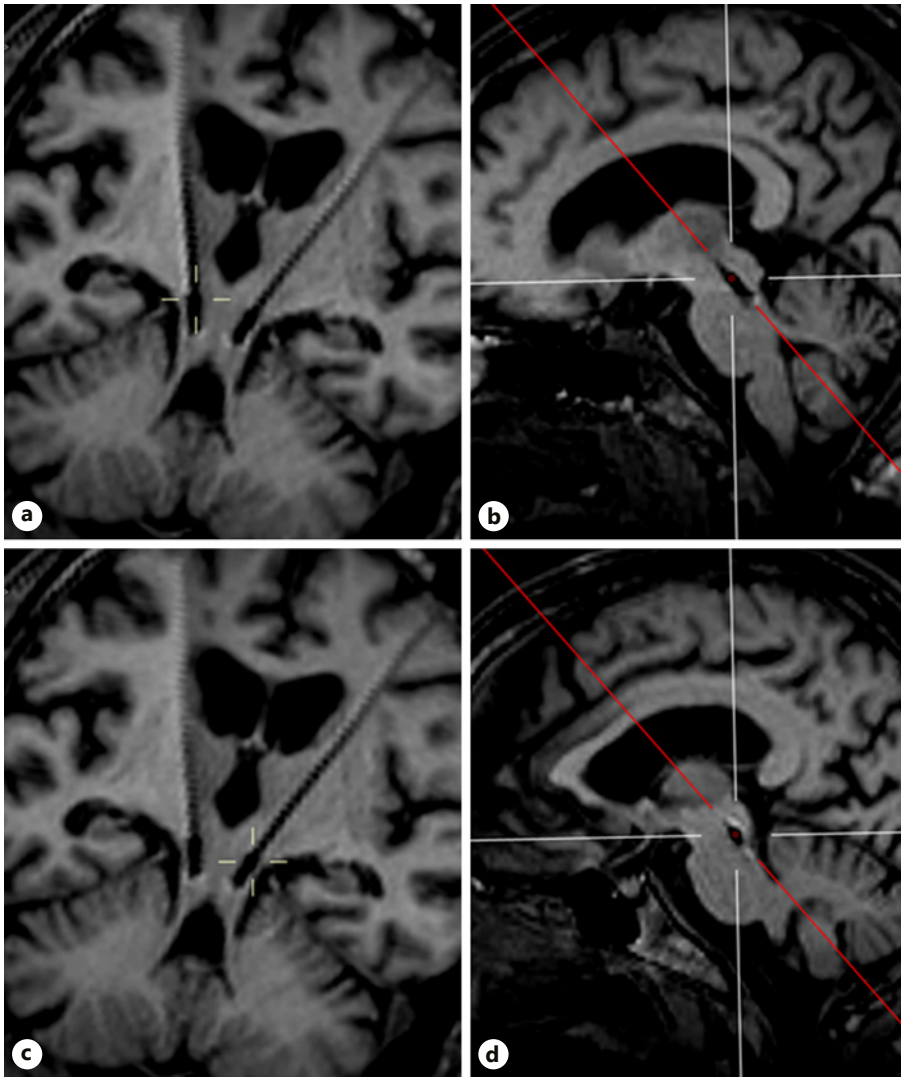

Fig. 1. T1-weighted MR images showing trajectory of bilaterally implanted PPN electrodes in patient 6. Coronal (**a**, **c**) and corresponding sagittal (**b**, **d**) views are shown, with markers centred at the active contact location. PPN, pedunculopontine nucleus.

3]. The outcomes, however, have not been consistently reproducible across treated cohorts. This may be partly attributable to variations in target selection within the PPN region, stimulation parameters, unilateral versus bilateral stimulation, isolated PPN stimulation versus combining the PPN with other targets (e.g., the pallidum or the subthalamic nucleus), duration of follow-up, disease progression, as well as variations in outcome measures used [3–7].

To take a few examples from the literature, the PPN has been stimulated at various frequencies between 5 Hz and 130 Hz [3, 4, 8]; monopolar stimulation has been used as well as bipolar stimulation [7–10]; and targeting has involved the anterior PPN, posterior PPN, rostral PPN, ventral PPN, cuneiform, the peripeduncular nucleus, the lemniscus and their surroundings [7, 11, 12]. Furthermore, some reports describe a significant improvement in the motor section of the Unified PD Rating Score (UPDRS-III) even when L-dopa only had a moderate or no effect [13]. PPN-DBS has also been described to improve REM sleep and cognition [14–16].

Presently, the number of published cases examining the effect of PPN-DBS in PD is nearly a hundred, comprising case reports and a few studies of less than 10 patients. There are fewer data available on atypical parkinsonian disorders such as progressive supranuclear palsy (PSP) [10, 17, 18]. Here, we present a descriptive case series summarizing the clinical outcomes of 6 patients treated with PPN-DBS at our centre and discuss the observed trends and potential avenues that may help further improve patient outcomes.

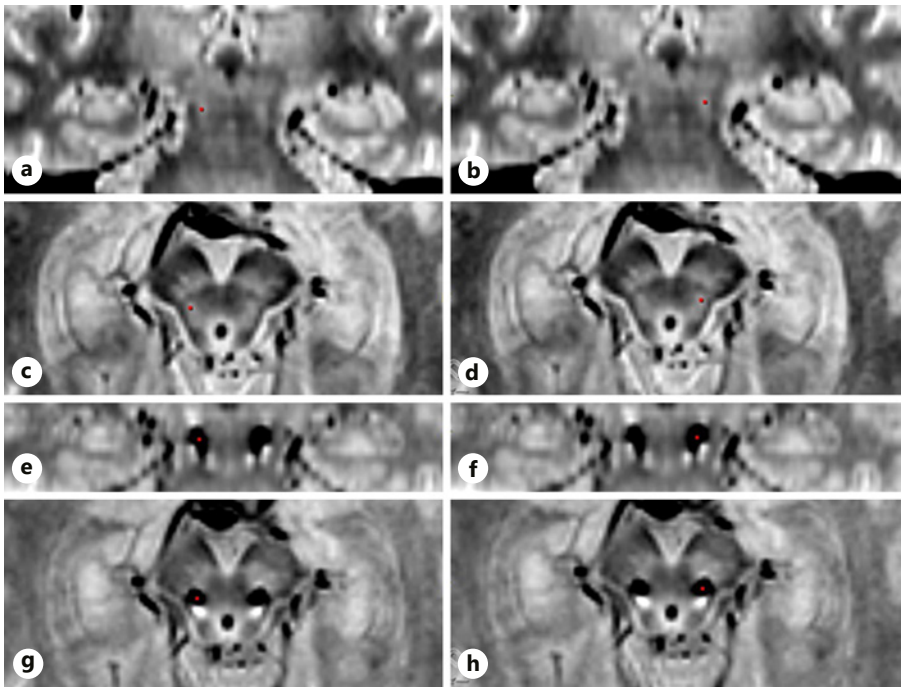

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Fig. 2. Proton density-weighted MRI for patient 6: right and left pre-operative coronal (**a**, **b**), axial (**c**, **d**) post-operative coronal (**e**, **f**), and axial (**g**, **h**). The red dot indicates the active contact in all images.

Methods

Six patients, 3 with PD and 3 with PSP, were treated with PPN-DBS for dopa-refractory FOG and falls at the National Hospital for Neurology and Neurosurgery between 2009 and 2016. Our strategy was aimed at generating additional pilot data to identify which symptoms/signs most consistently responded to stimulation of the PPN and whether unilateral or bilateral surgery was required. MRI-guided and MRI-verified surgery was performed under general anaesthesia according to our previously published stereotactic technique [19], using Medtronic 3389 electrodes and Activa PC™ devices. As fewer penetrations are intuitively safer, and (initially) unilateral PPN was thought likely to be sufficient due to its bilateral anatomical connections, the first 3 patients had unilateral implantation, the other 3 were bilateral.

The target was visualized on proton density stereotactic MRI showing the target area and its surroundings as previously described [20, 21]. Trajectories that did not penetrate the ventricle were chosen and electrode placement accuracy was confirmed by post-implant MRI.

Post-operative imaging confirmed successful placement of electrodes in the PPN region in all patients, as shown in representative images in Figures 1 and 2. All patients underwent initial stimulation programming in an iterative manner, to optimize gait freezing while avoiding adverse effects. Stimulation adjustments were attempted as required at each routine outpatient clinic visit.

For the PD group, on- and off-medication total UPDRS-III, composite gait score (UPDRS-III items 27–30: Arising from chair, Posture, Gait, and Postural instability), and UPDRS-II gait-related item subscores (13–15: Falling, Freezing, and Walking) were recorded. For patients with PSP, the total PSP Rating Scale (PSPRS) score, PSPRS gait section score (items 24–28), and history of falls frequency (PSPRS item 5) were recorded on usual medication. For all patients, the Freezing of Gait Questionnaire (FOG-Q) or Gait and Falls Questionnaire (GFQ) scores were recorded. All assessments were done pre- and post-operatively during follow-up visits.

Results

Table 1 summarizes patient characteristics, stimulation parameters, and clinical outcomes for the 6 patients. A synopsis of each is provided below:

Patient 1 was a right-handed 74-year-old man with PSP (pure akinesia and gait freezing phenotype) with an 8-year history of gradually worsening gait initiation difficulties and falls, marked micrographia and dysarthria. He displayed oculomotor signs consisting of slow saccades and macro square-wave jerks. He obtained no significant benefit from up to 800 mg per day of levodopa and amantadine. MRI showed mild midbrain atrophy and DaTscan imaging indicated bilateral dopaminergic nigrostriatal degeneration. The patient underwent left PPN-DBS (the more affected side). He reported subjective benefit in gait initiation and reduction in falls although this was not reflected in objective gait assessments scores which were worse 9 months post-operatively (Table 1).

Patient 2 was a 58-year-old woman with PSP (Richardson syndrome) presenting with gait initiation difficulties

Table 1. Summary of clinical outcomes of PPN-DBS-treated patients

Patient	Age at time of surgery, years	Sex	Diagnosis	Duration of symptoms at time of surgery	Unilateral or bilateral stimulation	Stimulation settings at time of assessment	Baseline (Pre-operative) assessments†	Post-operative assessments on stimulation†	Additional information, clinical impression/ subjective report of response, and adverse events
1	74	M	PSP (PAGF subtype)	8 years	Unilateral (L)	C+/1– 3.0 V 60 μs 20 Hz	Total PSPRS: 27 PSPRS gait score: 10 PSPRS item 5 (falls): 1	*At 9 months:* Total PSPRS: 31 PSPRS gait score: 13 PSPRS item 5 (falls): 0	Minor benefit reported in gait initiation. AEs: paraesthesias (lower limbs): Rt. > Lt.
2	58	F	PSP (RS subtype)	6 years	Unilateral (L)	C+/2– 1.6 V 60 μs 30 Hz	Total PSPRS: 50 PSPRS gait score: 15 PSPRS item 5 (falls): 4	*At 6 months:* Total PSPRS: 51 PSPRS gait score: 16 PSPRS item 5 (falls): 4	No immediate or delayed benefit noted Stimulation ON and OFF assessment at 6 months showed no change in gait AEs: oscillopsia, Rt leg tingling
3	71	M	PD	20 years	Unilateral (R)	0–, 1–/2+ 3.0 V 60 μs 30 Hz	UPDRS-III: 37/19 UPDRS-III items 27–30: 10/5 UPDRS-II items 13,14,15: 2, 2, 1	*At 9 months:* UPDRS-III: 40/35 UPDRS-III items 27–30: 10/10 UPDRS-II items 13,14,15: 2, 1, 1	Assessed in gait lab: no stimulation related benefit noted Stimulation ON and OFF assessment done at 6 months: no change noted in UPDRS-III items 27–30 composite score DBS subsequently turned off due to lack of perceptible benefit AEs: peri-oral paraesthesias urinary incontinence
4	68	M	PSP (parkinsonism subtype)	12 years	Bilateral	C+/1– 2.4 V 60 μs 20 Hz C+/9– 2.4 V 60 μs 20Hz	Total PSPRS: 39 PSPRS gait score: 13 PSPRS item 5 (falls): 3 FOG-Q: 20 GFQ: 43	*At 6 months:* Total PSPRS: 37 PSPRS gait score: 13 PSPRS item 5 (falls): 2 FOG-Q: 9 at *1 month* GFQ: 34 at *12 months*	Sustained and significant reduction in FOG reported throughout follow-up (last assessed 4 years post-op) AEs: Rt. sided ptosis, bilateral facial pulling
5	70	M	PD	20 years	Bilateral	C+/1– 2.0 V 60 μs 20 Hz C+/9– 2.0 V 60 μs 20 Hz	UPDRS-III: 50/23 UPDRS-III items 27–30: 8/6 UPDRS-II items 13, 14, 15: 4, 4, 3	[Not available]	At 6-month follow-up reported significant improvement in freezing (rare episodes) and falls; reduction in frequency of falls from 25–30 per day to average of <1/day Subsequent subjective deterioration, although 3 years after surgery had 3–4 freezing episodes/day and falls frequency remained <1/day AEs: paraesthesias Rt. Arm and face, somnolence, dizziness
6	73	M	PD	9 years	Bilateral	C+/3– 2.7 V 60 μs 20 Hz C+/11– 2.7 V 60 μs 20 Hz	UPDRS-III: 21/14 UPDRS-III items 27–30: 6/5 UPDRS-II items 13,14,15: 4, 4, 2 GFQ: 41	At 3 years*: UPDRS-III: 40/33 UPDRS-III items 27–30: 8/5 UPDRS-II items 13,14,15: 0, 2, 2 GFQ: 23	Reduced FOG and falls for 6 months post-op but had loss of effect by 12 months Regained benefit with cycling stimulation 3 years after surgery (see Table 2 for on/off stimulation assessments) AEs: bilateral lower limb paraesthesias

PPN, pedunculopontine nucleus; DBS, deep brain stimulation; PSP, progressive supranuclear palsy; PSPRS, PSP Rating Scale; FOG-Q, Freezing of Gait Questionnaire; PD, Parkinson's disease; UPDRS, Unified PD Rating Score; FOG, freezing of gait; GFQ, Gait and Falls Questionnaire. † UPDRS-III and UPDRS-III items 27–30 composite scores are reported in the OFF/ON medication states. All other scores are in the patients' usual ON medication state. * With diurnal cycling of stimulation.

and early postural instability and falls. She was found to have symmetrical parkinsonism with predominantly axial rigidity and vertical supranuclear opthalmoparesis. She also suffered from palilalia and later developed swallowing difficulties. Levodopa did not provide any significant benefit. Six years after symptom onset, she underwent left PPN-DBS. There was no subjective or objective benefit noted despite extensive attempts to optimize stimulation parameters. At 6 months post-operatively, stimulation on and off assessments indicated no stimulation-related benefit (Table 1).

Patient 3 was a 71-year-old man with PD and predominantly left sided involvement. He initially presented with hand tremor; symptoms gradually progressed with dopa-refractory freezing and falls at a levodopa equivalent daily dose (LEDD) of 1,400 mg. He underwent right PPN-DBS 20 years after symptom onset. Involuntary bladder emptying occurred during and after the neurosurgical procedure (reported in detail elsewhere) [22]. There was no improvement in FOG or falls assessments at 6 and 9 months post-operatively, including on and off stimulation comparisons using spatio-temporal gait analysis (Table 1). Stimulation was turned off after 5 years due to lack of any perceptible benefit.

Patient 4 was a 68-year-old man with a 12-year history of an akinetic rigid syndrome presenting with marked hypophonia and progressive slowness, FOG, postural instability, and falls. He was noted to have vertical supranuclear gaze palsy, reduced saccade velocity, and square-wave jerks. There was no improvement in gait symptoms with up to 1,200 mg per day of levodopa. MRI showed midbrain atrophy. After a diagnosis of PSP-P (parkinsonian subtype) he underwent bilateral PPN-DBS. A significant improvement in FOG was noted early in the post-operative course and was sustained until his last clinic follow-up at 4 years. This is reflected in FOG-Q and GFQ scores but contrasts with the minimal change seen on the PSPRS (Table 1).

Patient 5 was a 70-year-old man with PD with a 20-year history of symptoms, initially presenting with micrographia and hesitant speech, subsequently progressing to significant FOG and falls in the on-medication state (LEDD 930 mg). He underwent bilateral PPN-DBS. He declined to have objective post-operative assessments but during the 6-month post-operative clinic visit, he reported a dramatic reduction in frequency of falls from 25 to 30 per day to an average of <1 per day. There was subsequent deterioration after 9 months, but compared to pre-operative baseline, gait and balance remained improved 3 years after surgery (Table 1).

Table 2. Gait assessments for patient 6 done in the on-medication state with DBS on and off

Assessment	Off stimulation	On stimulation
UPDRS-III items 27–30	10	4
10-m SSW, time taken, min:s‡	4:35	0:45
10-m SSW, *n* freezes >2 s‡	25	1.3
360° turns [R + L], time taken, min: s‡	00:48	00:10
360° turns, *n* steps taken, R/L‡	14/12	4/4

DBS, deep brain stimulation; UPDRS, Unified PD Rating Score; SSW, sit-stand-walk. ‡ The mean of 3 independent measurements is reported.

Patient 6 was a 73-year-old man with a 9-year history of PD that responded to levodopa for the first 4 years, at which point he developed progressive medication refractory FOG (LEDD 900 mg). DaTscan imaging confirmed asymmetric dopaminergic nigrostriatal degeneration. Bilateral PPN-DBS 6-years after symptom onset provided a good initial response with significant reduction in FOG and falls frequency from 5 to 6 per day after 3 months. However, the beneficial effect subsequently declined, and at 12 months after surgery, symptoms were back to the pre-operative state. At the 3-year post-operative clinic visit, he reported regaining a marked improvement in gait and balance by turning off the stimulation overnight and keeping it on only during the day (Table 1). After 6 months of utilizing this technique daily and reporting sustained effects, an objective evaluation of gait was carried out in the stimulation on and off conditions and is presented below (Table 2; online Suppl. Video 1; see www.karger.com/doi/10.1159/000511978 for all suppl. material).

Patient 6: Gait Assessments after 6 Months of Diurnal Cycling Stimulation

The patient was on his usual medications and was not aware of whether the DBS device was on or off during the evaluation. The stimulation parameters were as listed in Table 1. UPDRS-III items 27–30 as well as more sensitive quantitative measures of freezing using a 10-metre sit-stand-walk (10-m SSW) and 360° spot turns in the on and off stimulation conditions were assessed [23, 24]. The 10-m SSW was timed and the number of freezing episodes greater than 2 s was counted. The 360° turns were done on the spot towards the right then left, with

the number of steps taken for completion in each direction and the total time taken reported. Three measurements in each DBS condition after at least 2 h of alternating between them were taken over a period of 2 days and averaged. Each assessment was done 1–1.5 h after a levodopa dose, and the on-medication state was verified with assessment of segmental motor signs in order to minimize the effect of levodopa-related fluctuations on gait assessments. Quantitative results are summarized in Table 2. A corresponding representative video demonstrating each assessment in the 2 DBS conditions is provided.

Discussion

Given the numerous variables surrounding the implementation of PPN-DBS, before embarking on a randomized controlled trial, our group wished to gather some initial open-label experience with PPN-DBS. As a result, our cohort comprises a mixture of 6 patients with PD and PSP, as well as unilateral and bilateral stimulation. While it is difficult to draw any definite conclusions from such a small, heterogeneous group, there are a number of interesting observations to be made.

All 3 of the bilaterally treated patients seemed to respond at least initially, while 2 of the 3 unilaterally implanted patients did not respond, with the remaining one having an equivocal response. While unilateral PPN stimulation has certainly been reported to produce beneficial effects on FOG and falls and is justified by the bilateral anatomical connectivity of the PPN and the increased surgical risk of bilateral implantation [4, 5], other reports that included both unilateral and bilaterally operated patients corroborate the notion that bilateral stimulation may be more effective [5, 6, 10].

Among PSP patients, another factor that may influence the degree of response to PPN stimulation is the subtype of the disorder. There have been multiple case reports of positive results in patients with PSP with predominant parkinsonism (PSP-P) [10, 25, 26]. However, a randomized trial of 8 patients with the Richardson syndrome subtype (PSP-RS) was negative [17]. While there is considerable overlap in these classifications particularly in later stages, factors such as disease duration and rate of progression that differ between these groups may reflect the observed outcomes. Indeed, among our 3 PSP patients, the clear responder (patient 4) had a protracted course of disease, while patient 2 who obtained no benefit had a more classical PSP-RS phenotype with a higher PSPRS score despite a shorter disease duration at the time of surgery.

Apart from the issue of heterogeneity of patients, electrode placement, and programming practices, reported outcomes of PPN-DBS in this cohort, as in much of the rest of the literature, are limited by the standardized outcome measures used, and in particular by the inherent lack of sensitivity of UPDRS and PSPRS and their respective gait-related item subscores in detecting changes in gait and freezing [3, 27]. Moreover, it should be noted that the original (non-MDS) version of UPDRS-III and PSPRS tools do not include any specific objective assessment of freezing, which is a major element of gait dysfunction expected to respond to PPN-DBS. Quantification of FOG has therefore often been reliant on the 5-category patient-reported item 14 of UPDRS-II in many reports. The GFQ has been shown to be more sensitive in detecting changes in FOG and falls after PPN-DBS in patients who had no change reflected in the UPDRS gait-related items [27]. Specialized spatio-temporal gait analysis, while more objective and detailed, can be significantly affected by the intermittent nature of FOG. The recognition of these limitations for objective assessment of FOG has led to recommendations of using repeated assessments with more sensitive clinical tools such as rapid 360° on-the-spot turns in both directions, and combining a gait trajectory with dual tasking if the former is negative [23, 24].

Limitations of this set of data in addition to those discussed previously include the open label design with non-blinded assessments, and some missing data with regards to post-operative assessments for patient 5 and GFQ scores. Nevertheless, this case series adds to the relatively scant literature of only a handful of studies with greater than 5 patients describing clinical outcomes of PPN-DBS and aids in advancing our understanding of this intervention from the collective patterns observed.

Additionally, case 6 illustrates the potential utility of using cycling in PPN-DBS to maintain improvements in gait and balance obtained from this treatment that may diminish over time with continuous stimulation in some patients. Patient 6 demonstrated a marked improvement in the 10-m SSW and 360° turn assessments with PPN stimulation on, and also had an improved GFQ score 3 years post-operatively despite an overall higher UPDRS-III. Habituation to DBS effects with continuous stimulation of certain DBS targets such as the ventral intermediate nucleus of the thalamus used for treating tremor is a well-recognized phenomenon, and diurnal cycling is commonly used to attenuate this [28, 29]. The loss of ben-

efit with continuous PPN stimulation such as that described in many of the initial responders in our cohort has been observed by others who have reported lack of a sustained effect in PPN-DBS-treated patients with long-term follow-up [5, 7, 10]. The utility of cyclic PPN stimulation in the daytime-on night-time-off configuration has previously been reported in order to reduce tolerance effects [7] although the benefit relative to continuous stimulation has not been explicitly quantified, while reports of the converse nocturnal-only stimulation have indicated potential benefits in non-motor but not motor symptoms [16, 30].

While the mechanism of this habituation effect and its apparent reversal with intermittent stimulation is not currently well understood, and the phenomenon is only demonstrable in the sole patient in our cohort still under active follow-up, the substantial and reproducible clinical benefit seen in this case 3 years following surgery despite disease progression makes it a strategy worth exploring in other patients treated with PPN-DBS, alongside refining processes of surgical targeting and patient selection to further define and improve the therapeutic application of this intervention. A progressive loss of effect cannot be ruled out over time, and more data are needed to confirm the utility of this approach.

In summary, the PPN remains an investigational target for DBS in patients with dopa-refractory FOG. This small case series corroborates some common features from the literature: patients with PSP-RS subtype are unlikely to benefit; bilateral stimulation may be superior to unilateral stimulation; and diurnal cycling of stimulation merits further investigation in PPN-DBS patients.

Statement of Ethics

All procedures described in this case report were carried out under the institution's usual standard of clinical care, and no experimentation was performed. The patients involved provided written informed consent for use of clinical information, images, and video media for publication.

Conflict of Interest Statement

The authors declare no conflict of interest relating directly to this manuscript. We declare the following financial and non-financial disclosures: V.D. has received honoraria and travel expenses from Boston Scientific. H.A. has received honoraria and travel expenses from Boston Scientific and BrainLab. P.L., L.Z., and M.H. have received honoraria and travel expenses from Medtronic and Boston Scientific for speaking at meetings. T.F. has received grant support from NIHR, John Black Charitable Foundation, Rosetrees Trust, Michael J. Fox Foundation, and Cure Parkinson's Trust. He has honoraria for speaking at meetings supported by Boston Scientific, BIAL, and Profile Pharma. He serves on advisory boards for BIAL, Oxford Biomedica, and Peptron.

Funding Sources

No funding was received for this work.

Author Contributions

Conception: T.F. and L.Z.; investigation and data collection: V.D., A.R., I.A.O., A.P., D.C., and B.D.; writing of original draft manuscript: V.D.; review and editing: T.F., L.Z., H.A., M.H., P.L., M.J., and J.H.

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