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Balance control systems in Parkinson's disease and the impact of pedunculopontine area stimulation

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Impaired balance is a major contributor to falls and diminished quality of life in Parkinson's disease, yet the pathophysiology is poorly understood. Here, we assessed if patients with Parkinson's disease and severe clinical balance impairment have deficits in the intermittent and continuous control systems proposed to maintain upright stance, and furthermore, whether such deficits are potentially reversible, with the experimental therapy of pedunculopontine nucleus deep brain stimulation. Two subject groups were assessed: (i) 13 patients with Parkinson's disease and severe clinical balance impairment, implanted with pedunculopontine nucleus deep brain stimulators; and (ii) 13 healthy control subjects. Patients were assessed in the OFF medication state and blinded to two conditions; off and on pedunculopontine nucleus stimulation. Postural sway data (deviations in centre of pressure) were collected during quiet stance using posturography. Intermittent control of sway was assessed by calculating the frequency of intermittent switching behaviour (discontinuities), derived using a wavelet-based transformation of the sway time series. Continuous control of sway was assessed with a proportional–integral–derivative (PID) controller model using ballistic reaction time as a measure of feedback delay. Clinical balance impairment was assessed using the 'pull test' to rate postural reflexes and by rating attempts to arise from sitting to standing. Patients with Parkinson's disease demonstrated reduced intermittent switching of postural sway compared with healthy controls. Patients also had abnormal feedback gains in postural sway according to the PID model. Pedunculopontine nucleus stimulation improved intermittent switching of postural sway, feedback gains in the PID model and clinical balance impairment. Clinical balance impairment correlated with intermittent switching of postural sway (rho = -0.705, $P < 0.001$) and feedback gains in the PID model (rho = 0.619, $P = 0.011$). These results suggest that dysfunctional intermittent and continuous control systems may contribute to the pathophysiology of clinical balance impairment in Parkinson's disease. Clinical balance impairment and their related control system deficits are potentially reversible, as demonstrated by their improvement with pedunculopontine nucleus deep brain stimulation.

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Abbreviations: DBS = deep brain stimulation; PID = proportional integral derivative; PPN = pedunculopontine nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Impaired balance is a major contributor to diminished quality of life in Parkinson's disease (Marras *et al.*, 2008). Balance impairment in Parkinson's disease leads to symptoms such as falls, a sense of unsteadiness when walking and difficulty transitioning between positions such as sitting to standing (Schoneburg *et al.*, 2013). Such symptoms are common at diagnosis and become more prominent and treatment refractory with disease progression (Kim *et al.*, 2013). However, the pathophysiology of such balance impairment in Parkinson's disease is inadequately understood. Deficits associated with balance impairment in Parkinson's disease have included cholinergic deficiency, impaired attentional processing, increased body rigidity, abnormal patterns of leg muscle recruitment and increased body sway (Muller *et al.*, 2013; Schoneburg *et al.*, 2013; Rinalduzzi *et al.*, 2015). However, the precise nature of the underlying network dysfunction that causes balance impairment is unclear.

Recently, analysis of postural sway has attempted to explore the underlying control systems proposed to maintain upright stance (Gawthrop *et al.*, 2014; Morasso *et al.*, 2014). Postural sway is the constant movement in centre of mass which occurs even during quiet standing (Winter *et al.*, 1990). This can be approximated using posturography, which involves standing on a pressure sensitive plate to track variations in centre of pressure (an approximation of centre of mass) (Rocchi *et al.*, 2006; Visser *et al.*, 2008). Maintenance of upright stance requires a constant and active process of leg muscle modulation, as ankle stiffness alone can be insufficient to counteract torque from gravity (Schoneburg *et al.*, 2013). This continuous process of maintaining centre of mass around a specific balancing point is reflected in postural sway and represents a control theory challenge, akin to regulating temperature with a thermostat or speed of a car with cruise control (Morasso *et al.*, 2014; Glasauer and Straka, 2017). Indeed, many of the models of biological control systems have developed along with those used in machines (Gawthrop *et al.*, 2014). It is important to stress that these control system models are conceptual representations that aim to capture brain function rather than recreate neural circuitry.

A long-held view is that postural sway is regulated by a continuous feedback controller, such as the proportional–integral–derivative (PID) model, where the state of the control variable (position of centre of mass) continuously updates the output (motor response) (Peterka, 2000, 2002). PID continuous controllers use information from three time domains regarding error in the control variable in order to shape the output (Aström and Murray, 2010). Present ('proportional') information reflects the current error (e.g. distance of centre of mass from the setpoint). Past ('integral') information accounts for accrued errors (e.g. from a previous lurch backwards) and helps avoid drift from the set point. Future ('derivative') information predicts the error of the current trajectory (e.g. over/undershoot) and helps reduce oscillations around the set point. Importantly, these three time factors are not treated equally, but are weighted by the system—and this weighting shapes the characteristics of control (e.g. how quickly deficits are made up and how much oscillation occurs). A range of indirect phenomena have suggested that continuous sway control systems may be affected in Parkinson's disease, for example the detection of abnormal resonance in sway including limit cycle oscillations (Maurer *et al.*, 2004; Chagdes *et al.*, 2016). However, there is a lack of research directly addressing whether PID error signal processing in the control of sway is affected by Parkinson's disease and its treatment.

In contrast, intermittent control has recently arisen as an attractive additional or alternative model to maintain sway, which may better account for the significant and variable feedback delays from neural processing, which would confound continuous control (Bottaro *et al.*, 2005, 2008; Gawthrop *et al.*, 2011; Loram *et al.*, 2011). Continuous and intermittent control systems are not mutually exclusive. For example, a process of continuous monitoring with intermittent responses has been postulated (Gawthrop *et al.*, 2011). Intermittent control of sway is proposed to involve the event triggered episodic release of ballistic, pre-programmed corrective responses (Bottaro *et al.*, 2005; Gawthrop *et al.*, 2014). Interestingly, the expression of such motor programmes may be impaired in patients with Parkinson's disease and axial deficits—evidenced by our previous finding that such patients fail to exhibit the 'Start-React' phenomenon (Thevathasan *et al.*, 2011*b*). 'Start-React' refers to the accelerated release of ballistic, pre-programmed movement in response to startling stimuli, such as very loud sounds (Valls-Sole *et al.*, 1999). Importantly, we found that Start-React in Parkinson's disease could be restored by pedunculopontine nucleus (PPN) deep brain stimulation (DBS). Thus, taken together, these findings raise the possibility of an associated impairment in the output of intermittent sway control, which may be

amenable to recovery, along with related clinical balance impairment.

Indeed, the reversal of balance impairment in Parkinson's disease has become a major therapeutic challenge. Conventional treatments for Parkinson's disease such as levodopa and subthalamic or pallidal DBS are often minimally effective or can even worsen balance (Hariz *et al.*, 2008; Visser *et al.*, 2008; St George *et al.*, 2010). PPN DBS therefore arose as an experimental therapy for otherwise refractory gait and balance impairment. Small clinical studies have found that PPN DBS can improve gait freezing and falls (Ferraye *et al.*, 2009; Moro *et al.*, 2010; Thevathasan *et al.*, 2011*a*; Welter *et al.*, 2015). However, it is unclear if the benefit of PPN DBS on falls is because of improved balance or due to less gait freezing or some other factor (Thevathasan *et al.*, 2018). Clinical studies of PPN DBS have detected little or no specific benefit on postural instability, as assessed by clinical scales such as the pull test (Ferraye *et al.*, 2009; Moro *et al.*, 2010; Thevathasan *et al.*, 2011*b*; Welter *et al.*, 2015). However, this may reflect a lack of sensitivity of the assessment tools particularly where statistical power was low. Thus currently, it is unknown whether PPN DBS improves balance in Parkinson's disease. The potential of any therapy to improve balance in Parkinson's disease would be important information, even if only to reveal a viable therapeutic mechanism.

In this study, we acquired posturography data from patients with Parkinson's disease severely affected by clinical balance impairment, whilst off and on PPN DBS and compared results to healthy controls. Novel analysis methods were applied to derive measures of control system performance. We hypothesized that balance impairment in Parkinson's disease is associated with deficits in intermittent and continuous sway control and that these deficits would improve with PPN DBS. We also assessed if balance control system metrics correlated with clinical balance impairment, and thus may have potential as biomarkers.

Materials and methods

Subjects and clinical assessments

Two subject groups were assessed: (i) 13 patients (10 males) with Parkinson's disease complicated by severe clinical balance impairment, chronically implanted with bilateral PPN stimulators; and (ii) 13 age and gender matched (10 males) healthy controls. The two groups did not differ in age (70.0 ± 6.95 versus 69.8 ± 5.57 years; $U = 183.5$, $P = 0.699$). Subjects were recruited from centres in Oxford (England, UK), and Brisbane, Sydney and Melbourne (Australia). Data were collected over a 7-year period from December 2009 to December 2016. A database identified 28 patients implanted with bilateral single target PPN DBS for Parkinson's disease across the centres during the assessment period (up to March 2011 in Oxford and December 2016 in Australia). All patients were considered for inclusion and patients were not selected based on their benefit from DBS. Twelve patients were not assessed with posturography because of: death ($n = 1$), device explantation due to lack of efficacy ($n = 1$), dementia/frailty ($n = 4$), living in a remote location ($n = 4$), or involvement in other research ($n = 2$). Posturography was performed in 16 patients. Incomplete data from three patients were rejected before analysis. Of the 13 patients included, clinical outcomes of eight and reaction times of seven are previously reported (Thevathasan *et al.*, 2010, 2011*a*, *b*, 2012*a*). Ethics committee approval was obtained from all centres and participants gave written informed consent. Clinical details of the Parkinson's disease patients are shown in Table 1.

Patients with Parkinson's disease were selected for PPN stimulation because of severe gait freezing and postural instability persisting even ON medication, causing frequent falls. The persistence of these deficits despite adequate dopaminergic medication was determined clinically, via examination in a practically defined ON medication state (Thevathasan *et al.*, 2018). This was the dominant symptomatic issue at surgery and motor fluctuations, if present, were not severe. In Parkinson's disease, gait freezing and postural instability become more common and less medication responsive with disease progression (Giladi *et al.*, 2001*a*; Bloem *et al.*, 2004). However, it is unusual in Parkinson's disease for severe ON medication gait freezing and postural instability to be the predominant issue (Factor, 2008; Jankovic, 2008). As there is no definitive test for Parkinson's disease in life, we stress that the diagnosis of Parkinson's disease here is presumptive.

Patients with Parkinson's disease were receiving lone bilateral stimulation to the caudal PPN region, without implantation of other targets (Hamani *et al.*, 2016*b*). Surgical implantation of the PPN from two of the centres has been described previously (Pereira *et al.*, 2008; Thevathasan *et al.*, 2011*b*). Figure 1 demonstrates the stimulation locations (midpoint between active contacts for bipolar stimulation and cathodes for monopolar). Contacts were identified on postoperative CT fused with preoperative MRIs and referenced to local landmarks in the brainstem as described previously (Ferraye *et al.*, 2009). Coordinates were calculated as follows: laterality from midline (mean 6.481 mm, range 2.465–8.670 mm), ventrodorsal distance (d) from floor of the fourth ventricle (mean 6.403 mm, range 4.050–9.160 mm), and rostro-caudal distance (h) from a pontomesencephalic line connecting the pontomesencephalic junction to the inferior colliculi (mean −6.136 mm, range −2.185 to −12.544 mm). Chronic stimulation parameters were as follows: frequency 30 Hz (except one patient: 40 Hz), voltage range 2.5–4.9 V and pulse width 60 µs (except one patient: 90 µs).

Patients prospectively completed the Gait and Falls Questionnaire (GFQ, score/64), which assesses parkinsonian freezing, festination and falls (Giladi *et al.*, 2000). The Freezing of Gait Questionnaire (FOGQ, score/24) and Falls Question (FallsQ, score/4) are components of the GFQ (Giladi *et al.*, 2000, 2009). These questionnaires were administered prior to surgery and on the day of experiments and reflected function in patients' usual environments and medication states in the preceding weeks. Cognition was assessed with the Mini-Mental State Examination (score/30).

Experiments

In patients with Parkinson's disease, assessments were performed after overnight withdrawal of dopaminergic

Table 1 Parkinson's disease patients with balance impairment and PPN DBS

Patient	Age/ gender	Centre	PD duration, years	MMSE	UK Brain Bank criteria	LED (postop)	UPDRS III off/on meds (postop)	IT27–30 off/on meds (postop)	PPN DBS duration, years, months	GFQ pre/ postop	FOG pre/ postop	Falls Q pre/ postop	Clinical balance impairment (off/on DBS)
1	61 F	Brisbane	10	30	D,A,P	800	40/23	10/9	2, 0	61/36	24/16	4/3	5/4
2	72 M	Brisbane	18	30	D,A,T,P	2500	25/17	6/6	2, 6	30/16	14/11	4/2	3/3
3	76 M	Brisbane	6	28	A,P	600	26/14	6/4	2, 0	51/18	22/7	3/3	2/1
4	72 F	Brisbane	10	28	A,T,P	950	38/22	11/8	2, 0	48/26	22/13	4/2	5/3
5	71 M	Brisbane	4	29	D,T,P	1550	27/18	5/5	0, 6	48/21	18/9	4/3	2/2
6	77 M	Brisbane	6	30	A,P	1400	31/17	10/10	0, 6	31/14	16/6	1/2	5/5
7	56 M	Oxford	20	30	D,A,P	850	51/19	8/6	1, 0	38/40	14/15	4/4	3/2
8	78 F	Brisbane	11	27	A, T, P	1450	26/10	13/5	0, 7	46/30	20/16	4/3	^/^
9	74 M	Brisbane	9	30	A,T,P	1200	54/42	8/5	4, 6	^/37	^/15	^/3	4/3
10	75 M	Sydney	12	26	A,T,P	1200	32/24	7/6	1, 4	^/26	^/14	^/1	4/3
11	72 M	Brisbane	8	30	D,A,P	800	33/25	6/4	2, 7	^/20	^/8	^/2	3/1
12	62 M	Brisbane	14	29	D,A,T,P	800	38/28	5/5	4, 5	^/32	^/11	^/3	2/2
13	64 M	Melbourne	9	28	D,A,T,P	1000	44/26	6/4	5, 0	^/47	^/19	^/4	3/3

Postoperative (postop) clinical assessments were performed on the same day as experiments.

^ = not known; Clinical balance impairment (score/8) representing summation of UPDRS items of chair rise (item 27; score/4) and the pull test (item 30; score/4); FallsQ = Falls Question (score/4); FOGQ = Freezing of Gait Questionnaire (score/24); GFQ = Gait and Falls Questionnaire (score/64); IT27–30 = items 27–30 of UPDRS, assessing gait, posture and balance (score/16); MMSE = Mini Mental State Examination (score/30); UK Brain bank criteria: D = dyskinesias; A = asymmetry persistent; T = tremor at rest; P = progressive disease course; UPDRS III = part III (motor) of the Unified Parkinson's Disease Rating Scale (score/108).

LED = L-DOPA equivalent dose, mg/day.

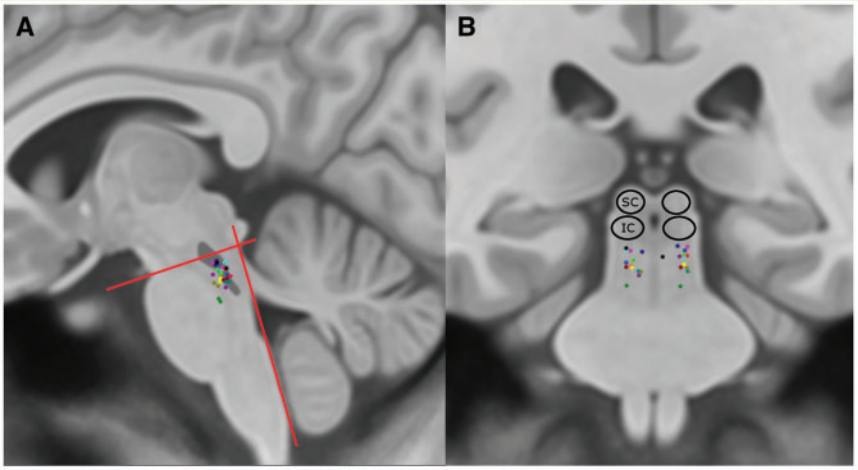

Figure 1 Localization of stimulation locations (coloured dots) represented in Montreal Neurological Institute (MNI) space (sagittal and coronal views). The relative location/extent of the pedunculopontine nucleus has been outlined on the sagittal view, based on cholineacetyltransferase immunohistochemical (ChAT5) staining in the human. Coordinates were calculated in millimetres from midline (laterality), ventrodorsal distance (d) from floor of the fourth ventricle and rostro-caudal distance (h) from a pontomesencephalic line connecting the pontomesencephalic junction to the inferior colliculi caudal margin, as described previously (Ferraye *et al.*, 2009). The mean (ranges) of these stimulation site coordinates were as follows: laterality 6.481 mm (2.5 to 8.7 mm), ventrodorsal distance (d) 6.4 mm (4.1 to 9.2 mm), rostro-caudal distance (h) 6.1 mm (−2.2 to −12.5 mm). IC = inferior colliculus; PM = ponto-mesencephalic line connecting the pontomesencephalic junction to the caudal end of the inferior colliculi; SC = superior colliculus.

medication and after 12 h of PPN DBS washout. Patients were assessed during two conditions, presented in counterbalanced order (using the Latin square method): Off PPN DBS and on bilateral PPN DBS. Patients were blinded to condition. The effectiveness of blinding was assessed in seven patients who were unable to guess the condition of stimulation better than chance after the wash-in period. Choice of contacts and stimulation parameters were as used for chronic therapy. After changing stimulation, a minimum 30 min wash-in period was enforced between conditions. Data were acquired using the same equipment and recording parameters across sites.

All posturography was performed using an AccuGait force-plate and accompanying NetForce Software (AMTI) with a measurement resolution of 0.003 N. Subjects were instructed to stand on the force-plate with eyes focussed on a wall mounted marker 1.5 m ahead. Feet were placed symmetrically across standardized markings on the force-plate. Distractions were minimized, and subjects requested not to talk. After the researcher observed that a state of quiet and stable stance had been achieved, data were acquired in 30-s trials. Four trials were obtained per condition. Patients were permitted to get off the force-plate and rest between trials if necessary to reduce fatigue. During experiments, one researcher (W.T. or J.L.T.) supervised proceedings, and monitored patient safety and altered stimulation. A second, blinded researcher operated the force-plate system and tagged the data according to the order of condition.

In a subgroup of eight patients with Parkinson's disease, a warned simple reaction time task was administered, providing an estimate of feedback delay for the PID model. As described and reported in seven of the patients previously, the task consisted of the serial presentation of 35 trials, each consisting of an auditory warning cue (92 dB, 40-ms duration, 300 Hz) followed (after a variable interval) by the auditory imperative 'go' cue (40-ms duration, 1000 Hz) (Thevathasan *et al.*, 2011*b*). The imperative stimulus was either normal intensity (89 dB) or loud (122 dB). Normal intensity trial results were used in analyses here. Patients were seated comfortably in a quiet room and instructed to react as quickly as possible with ballistic elbow flexion. Stimuli were controlled through a digital to analogue converter (1401, Cambridge electronic design). Auditory tones were delivered binaurally through headphones (Audio Technica ATH-ES7). Reaction times were assessed with a triaxial accelerometer taped to the radial styloid. Data were sampled at 256 Hz (Porti amplifier, TMSI). Accelerometry (TMSI) was band-pass filtered between 2 and 60 Hz.

Patients with Parkinson's disease were clinically assessed using the motor subsection (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS, score/108), rated unblinded by the same neurologist or physiotherapist specialized in movement disorders (W.T., J.L.T.).

Anonymized data were transferred to a single centre (Bionics Institute) where researchers blinded to stimulation condition computed parameters using custom scripts in MATLAB (MathWorks Inc., Massachusetts, USA). Conditions were then revealed to permit statistical analysis.

Parameters and data analysis

Prior to analysis, all force-plate raw time series data were band-pass filtered between 0.001 and 10 Hz. For all sway values, the mean of the four trials per condition was used in statistical analysis.

The primary outcome measure was the frequency of intermittent switching in postural sway. Switching behaviour reflects abrupt changes or discontinuities in the preceding linear trajectory of the sway path when viewed at a particular time scale (Mosterman and Biswas, 1998). For example, this

may reflect switching between one subsystem of control to another. Intermittent switching of postural sway was calculated according to a published algorithm designed to detect such behaviour in posturography datasets based on a combination of wavelet analysis and Hilbert transformation (Nema *et al.*, 2017). This included (i) decomposing the filtered posturography time series data using a Daubechies wavelet transform. Like Fourier transformation, wavelet transforms extract temporal and frequency characteristics of time series. Wavelet analysis is particularly beneficial to analyse signals where frequency components vary over time. A relative strength of the Daubechies technique is to identify signal discontinuities; (ii) low-energy components were attenuated to reduce noise before reconstructing the components to obtain a filtered version of the original signal; and (iii) applying a Hilbert transform of the filtered signal to compute a time-frequency representation of the sway where discontinuities manifest as prominent peaks (Nema *et al.*, 2017). These peaks represent instances where intermittent changes (rapidly arising redirections of sway) had occurred. Peaks occurring above a threshold were counted to yield the rate of intermittent switching of postural sway (represented as Hz). The threshold was set at 10% of the standard deviation (SD) above the signal floor—a level determined after direct visualization of the dataset as best able to capture peaks in instantaneous frequency due to their large variance in amplitude (Supplementary Fig. 1). The amplitude of each peak represents the instantaneous frequency at the switching moment and has no clear physical meaning when considering complex multicomponent signals such as postural sway (Boashash, 1992). Thus, amplitude was not measured as an endpoint in its own right.

Sway data were also analysed according to a continuous PID control model in a subgroup of eight patients (where reaction time was available) in addition to the healthy controls using a custom script developed in MATLAB according to the following established method where standing is considered analogous to an inverted pendulum (Hidenori and Jiang, 2006) (Fig. 2). Assumptions included using ballistic elbow reaction time as a measure of delay in feedback control and that the body was rigid (without pivot points around limb or axial joints). Ballistic elbow flexion was considered a reasonable estimate of postural reaction times given its strong reticulospinal innervation (Lawrence and Kuypers, 1968; Carlsen *et al.*, 2009*a*). Patient height (measured in millimetres) was used to convert sway data to angular displacement according to trigonometry. The resultant parameters were gains in time domains of future, present and past scaled in arbitrary units (AU). To facilitate statistical analysis, we normalized these values in the Parkinson's disease patients relative to the data for healthy controls and expressed the difference as a percentage. The mean of each percentage (future, present and past) yielded a single value of PID model function for each patient/condition relative to healthy controls.

We computed standard measures of sway using custom scripts written in MATLAB. Two parameters were derived: (i) C90 area, which represents the area of an ellipse (measured in millimetres squared) that encompasses 90% of data points; and (ii) sway velocity, which represents the mean of the differentiated force-plate time series.

For the reaction time data, analysis was automated by a script developed in MATLAB including initial baseline removal (time constant individualized for each trial from the average baseline level 0.45 ms prior to the imperative) before rectification. The first five trials were rejected as practice. Response onset was defined as an amplitude rise exceeding the mean of the prestimulus (0.5 s) baseline by 3 SD. The mean normal intensity (89 dB) reaction time was used in statistical analysis.

For the clinical data, items of the UPDRS part III yielded two subscores (Fahn *et al.*, 1987). First, a balance subscore (score/8) representing summation of UPDRS items of chair rise (item 27; score/4) and the pull test (item 30; score/4). Second, the UPDRS item representing gait (item 29; score/4).

Statistical analysis

Given the small sample sizes, we adopted conservative non-parametric tests. Differences between subject groups were assessed with the Kruskal-Wallis test and *post hoc* Mann-Whitney U-test. Differences in patients with Parkinson's disease between conditions (on versus off PPN DBS) were assessed with the Wilcoxon signed ranks test. *Post hoc* tests were corrected for multiple comparisons using the false discovery rate (FDR) procedure (Bejamini and Hochberg, 1995). Level of significance was $P < 0.05$.

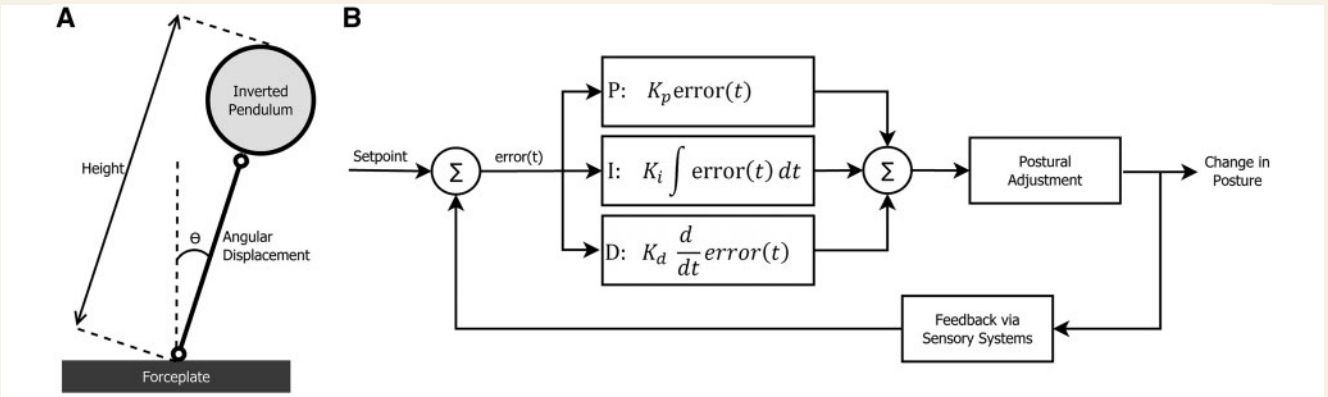

Figure 2 Schematic showing the inverted pendulum model of human balance (A) used in the PID control system (B). The setpoint input of the PID controller is fixed at zero and acquired posturography time-series data (converted to angular displacement using participant's height) gives the output allowing estimation of the factors K_p (proportional), K_i (integral) and K_d (derivative).

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Control system primary outcomes

Intermittent switching of postural sway

There was a significant difference in intermittent switching of postural sway between groups [$\chi^2(38) = 10.292$, $P = 0.006$] (Figs 3A and 4). *Post hoc* tests revealed that Parkinson's disease patients off DBS had reduced intermittent switching of postural sway compared to healthy controls (1.908 Hz versus 2.517 Hz, U = 230, $P = 0.016$). PPN DBS significantly increased intermittent switching of postural sway (1.908 Hz versus 2.350 Hz, W = 8, $P = 0.016$). This meant that intermittent switching of postural sway in Parkinson's disease patients when on DBS did not differ from healthy controls (2.350 Hz versus 2.517 Hz, U = 185, $P = 0.703$).

Gains in the PID model

There was a significant difference in PID model gains between groups [$\chi^2(28) = 6.199$, $P = 0.045$]. *Post hoc* tests revealed that Parkinson's disease patients off DBS were significantly different in PID model gains compared to healthy controls (difference 27.446%, U = 107, $P = 0.010$). PPN DBS significantly improved PID model gains towards normal (difference 5.016% versus difference 27.446%, W = 35, $P = 0.016$). This meant that the PID model gains were not different between Parkinson's disease patients when on DBS and healthy controls (difference 5.016%, U = 135, $P = 0.587$). Looking at each PID time factor individually revealed that PPN DBS increased past (1.797×10^{-5} versus 3.654×10^{-5}, W = 3, $P = 0.039$), reduced present (0.957 versus 0.902, T = 35, $P = 0.016$), and reduced future (9.938 versus 7.268, W = 34, $P = 0.023$) PID gains towards values seen in healthy controls (Fig. 3D–F).

Secondary outcomes

Sway area and velocity

There was a significant difference in C90 area between groups [$\chi^2(38) = 23.494$, $P < 0.001$]. *Post hoc* tests revealed that Parkinson's disease patients off DBS had larger C90 areas compared to healthy controls (109.899 mm^2 versus 21.451 mm^2, U = 95, $P < 0.001$). PPN DBS did not change C90 area (93.094 mm^2 versus 109.899 mm^2, W = 58, $P = 0.5$). This meant that C90 area remained significantly larger in Parkinson's disease patients when on

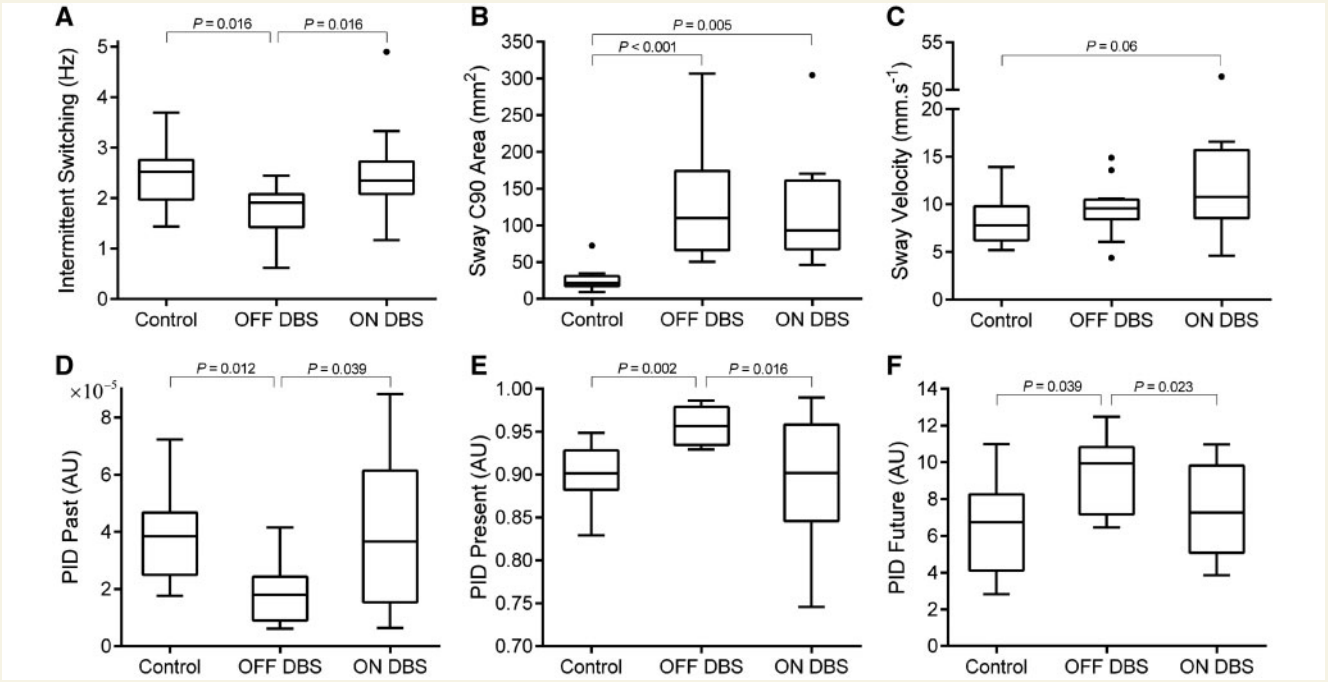

Figure 3 Postural sway parameters (medians and interquartile ranges) for healthy controls and Parkinson's disease patients (off and on PPN DBS). (**A**) Intermittent switching (abrupt, high amplitude redirections) of postural sway. (**B**) Sway C90 area (of an ellipse measured in millimetres squared that encompasses 90% of data points). (**C**) Sway velocity (mean of the differentiated time series). (**D**–**F**) PID continuous control model gains in time domains of past (**D**), present (**E**) and future (**F**) scaled in arbitrary units (AU). Differences between groups and conditions are indicated by bridges with *P*-values.

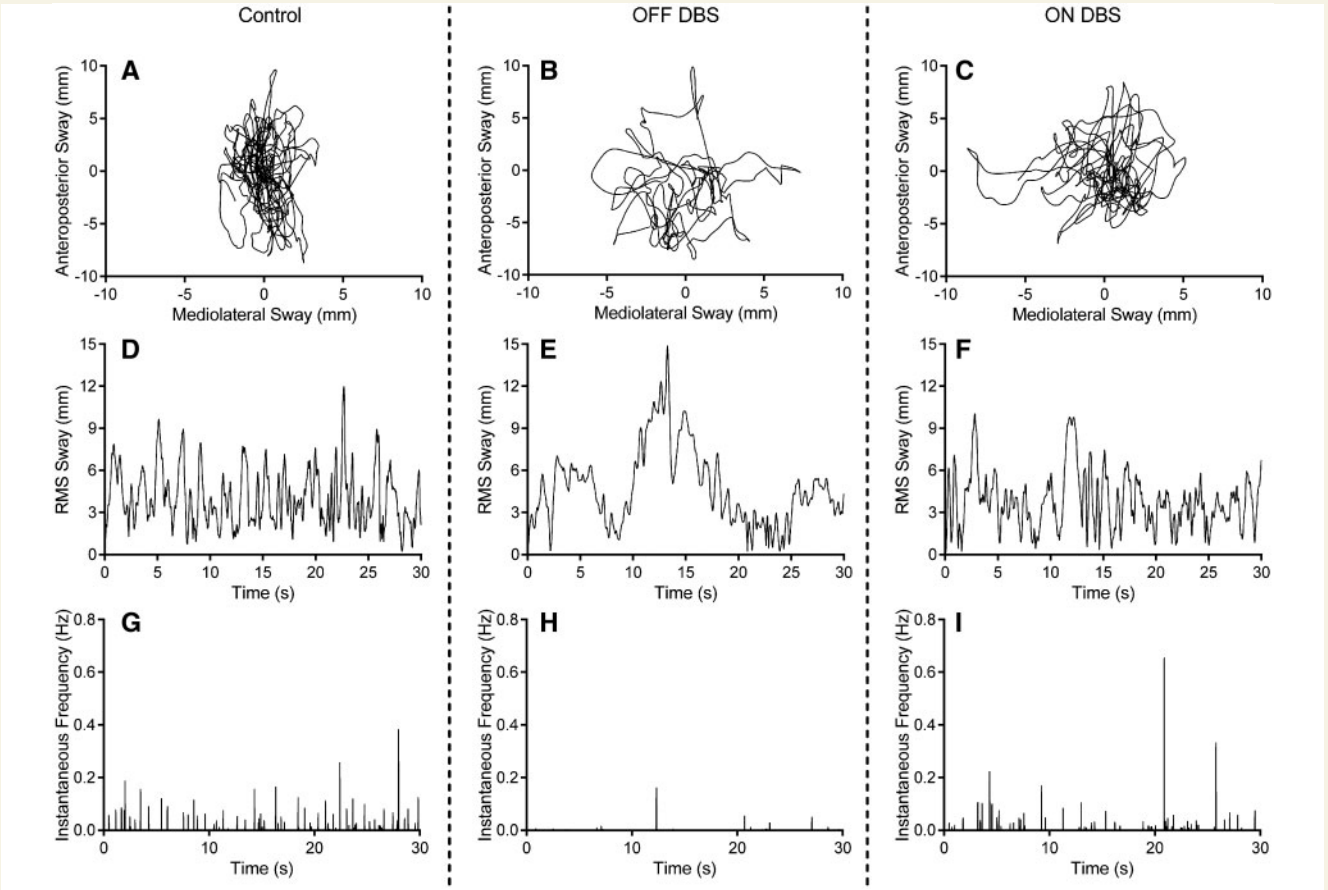

Figure 4 Example postural sway traces of a healthy control subject and Parkinson's disease Patient 5 (off and on PPN DBS) acquired during quiet stance on a force-plate (30-s trial). (**A**–**C**) Panels show movements in centre of pressure in two planes. Patients with Parkinson's disease have increased sway area but this did not change with PPN DBS. (**D**–**F**) Root mean square (RMS) of sway in millimetres. (**G**–**I**) The results of the wavelet-based transformation of the RMS sway time series with intermittent switching behaviour (abrupt redirections) clearly evident as instances of high frequency arising from the baseline.

PPN DBS compared with healthy controls (93.094 mm^2 versus 21.451 mm^2, U = 94, $P = 0.005$) (Figs 3B and 4).

There was no significant difference in sway velocity between groups [$\chi^2(38) = 4.931$, $P = 0.085$]. However, *post hoc* tests revealed a strong trend for PPN DBS to increase sway velocity (9.573 mm/s off DBS versus 10.785 mm/s on DBS, W = 16, $P = 0.060$] (Fig. 3C).

Correlations between sway parameters

Intermittent switching of postural sway correlated significantly with PID factors past (rho = 0.603, $P = 0.015$), present (rho = −0.829, $P < 0.001$) and future (rho = − 0.659, $P = 0.007$). There was a trend suggesting a positive correlation between intermittent switching and sway velocity (rho = 0.401, $P = 0.053$). There was no correlation between intermittent switching of postural sway and C90 area ($P = 0.106$).

Clinical measures

PPN DBS significantly improved the clinical balance score (expressed as mean/median) (3.417/3.000 off DBS versus 2.667/3.000 on DBS, W = 28, $P = 0.016$) but not the UPDRS gait subscore (2.417/2.000 off DBS versus 2.083/2.000 on DBS, W = 10, $P = 0.125$).

Correlations of clinical measures with sway parameters

The clinical balance score correlated significantly with intermittent switching of postural sway (rho = −0.735, $P < 0.001$) and overall PID gains (rho = 0.619, $P = 0.011$) (Fig. 5). There was no correlation between clinical balance score and C90 area ($P = 0.408$) or sway velocity ($P = 0.179$). Interestingly, the UPDRS gait score also correlated significantly with intermittent switching of postural sway (rho = −0.414, $P = 0.045$) but did not correlate with overall PID gains (rho = 0.096; $P = 0.726$) (Fig. 5).

Stimulation location

Stimulation locations varied considerably (Fig. 1), particularly in depth (h-value; mean −6.136 mm, range −2.185 to −12.544 mm) and extending beyond where immunohistochemistry is reported to have identified cholinergic neurons

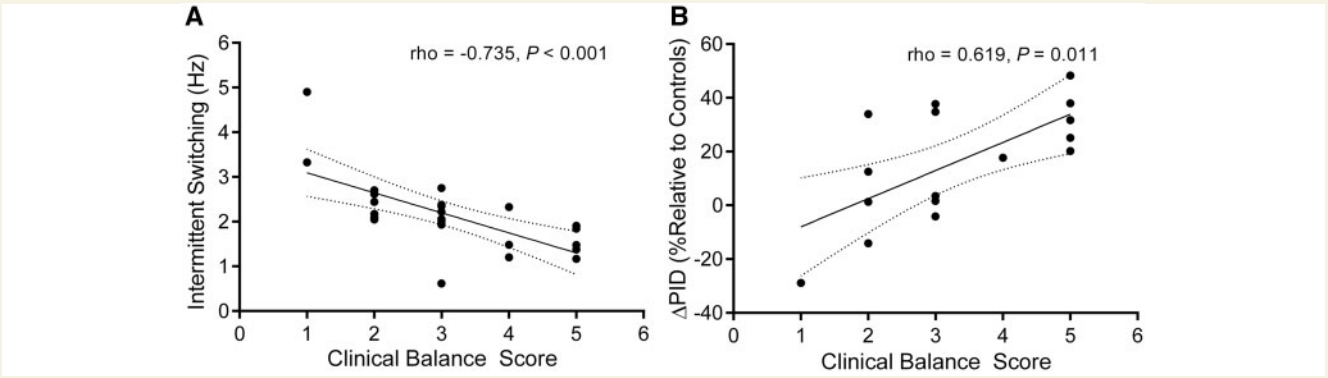

Figure 5 Correlations between clinical balance impairment and control system metrics. Correlations between clinical balance impairment (score/8), which represents summation of UPDRS items of chair rise (item 27; score/4) and the pull test (item 30; score/4) with measures of intermittent and continuous control of sway, namely: (**A**) intermittent switching (more switching behaviour correlates with lower balance impairment); and (**B**) the difference in normalized PID values relative to healthy controls (lower PID model gains relative to controls correlates with lower balance impairment).

(and, by inference, PPN location) in post-mortem samples (Mesulam *et al.*, 1989; Manaye *et al.*, 1999). However, we found no correlation between h-value (averaged per patient between the two sides) and intermittent switching of postural sway (rho = 0.451; $P = 0.125$) or clinical balance score (rho = 0.268; $P = 0.399$). Furthermore, we found no difference between patients with stimulation sites within the PPN region (defined as h-value between +2 and −6) and those with stimulation sites outside this region regarding the impact of DBS on intermittent switching of postural sway (50.847% improvement within the PPN versus 31.724% outside the PPN, U = 32, $P = 0.181$) or clinical balance score (10.000% reduction within the PPN versus 14.286% outside the PPN, U = 30, $P = 0.747$).

Discussion

In this study, we found that patients with Parkinson's disease and severe clinical balance impairment demonstrated reduced intermittent switching of postural sway compared with healthy controls. Patients with Parkinson's disease also had abnormal feedback gains according to a PID model of continuous control. Intermittent switching of postural sway and gains in the PID model were returned to normal values by PPN DBS. However, PPN DBS improved but did not resolve clinical balance impairment (summed UPDRS items for arising from a chair and the pull test). Clinical balance impairment correlated substantially with both intermittent switching of postural sway (rho = −0.735) and gains in the overall PID model (rho = 0.619). Intermittent switching of postural sway and gains in the PID model were highly correlated. However, we found no correlation between control systems measures and sway area. In patients with Parkinson's disease, sway area was significantly greater than in healthy controls but did not change with PPN DBS. Sway velocity in patients with Parkinson's disease did not differ from healthy subjects. Neither sway area nor sway velocity correlated with clinical balance impairment. The location of stimulation in the PPN region varied greatly in rostro-caudal location between patients. Despite this variance, we found no correlation between stimulation depth and the therapeutic impact on sway control systems or on clinical balance impairment.

First, we acknowledge limitations and potential confounds in this study. It should be noted that the control models we refer to are conceptual representations of brain functioning that aim to capture performance of the actual underlying neural circuitry. This is particularly true of the PID parameters, which were derived by assessing conformance of the raw sway data to the model and assumptions that elbow flexion reaction time reflected postural feedback delays and the body acted as a rigid inverted pendulum (Peterka, 2002; Hidenori and Jiang, 2006). However, intermittent switching of postural sway was derived solely from the postural sway data with a time-frequency representation (via wavelet analysis) (Nema *et al.*, 2017). This yielded information of when switching behaviour (abrupt redirections) were detected in the continuous sway pattern. The occurrence of these sudden changes to sway are real but it is an assumption that these represent the function of an underlying intermittent control system. The sample size of patients here is modest; however, this represents a large cohort of patients implanted with PPN DBS, and required 7 years to recruit between multiple centres. Only around 100 patients with PPN DBS have been reported in the literature (Thevathasan *et al.*, 2018). Selection bias may have influenced results; however, we did not attempt to 'enrich' the cohort by selecting patients based on their response to DBS. We included almost half of the implanted cohort available across the study centres. Disease-related events that prevented assessment such as dementia, frailty and death are not unexpected given the prognosis of Parkinson's disease especially where associated with severe axial deficits (Hely *et al.*, 1999). Patients implanted

with PPN DBS are a highly selected and unusual subgroup of patients with Parkinson's disease who suffer severe gait freezing and postural instability as their predominant form of motor impairment, so these results may not be completely generalizable to the Parkinson's disease population as a whole. Assessment of the clinical impact of PPN DBS was measured by retrospective use of UPDRS items that suffer limited scaling and reliability, and more comprehensive tools to assess balance impairment are now available (Bloem *et al.*, 2016). The scoring of clinical endpoints was performed by unblinded clinicians. However, patients in this study were blinded to the condition of stimulation and postural sway analysis was performed by a computer algorithm and blinded researchers.

Balance impairment in Parkinson's disease

This study suggests that dysfunction in sway control systems contributes to the pathophysiology of balance impairment in Parkinson's disease and is potentially reversible with therapy, at least in patients similar to those studied here. It has been relatively unexplored whether such control systems are dysfunctional in Parkinson's disease and contribute to the pathophysiology of balance impairment (Maurer *et al.*, 2004; Yamamoto *et al.*, 2011; Chagdes *et al.*, 2016). Here, we explicitly measured feedback gains according to the PID model of continuous control and calculated the frequency of intermittent switching behaviour in the sway dataset (Hidenori and Jiang, 2006; Nema *et al.*, 2017). We found that in healthy controls and Parkinson's disease patients, gains in PID model factors future and present were greatest with relatively little input from factor past—as previously reported in healthy subjects (Peterka, 2002; Masani *et al.*, 2006). This reliance on present and future and not past error information (i.e. proportional-derivative rather than proportional-integral-derivative control) could prioritize the damping of oscillations over the diminution of steady state error. Such proportional-derivative control of sway has been argued to be sufficiently effective while less computationally demanding (Masani *et al.*, 2006). We found that in Parkinson's disease compared to healthy subjects, the gains in future and present factors were increased and restored to normal levels by PPN DBS. For intermittent control, we found that in healthy subjects, intermittent switching of postural sway occurred at median 2.517 Hz. This is a similar value to a study reporting that in control of a virtual load, intermittent taps of a joystick were optimally deployed at a rate of around 2 Hz (Loram *et al.*, 2011). Here, we found that in patients with Parkinson's disease and balance impairment, intermittent switching of postural sway was reduced to median 1.908 Hz and restored by PPN DBS to median 2.350 Hz.

Thus, it may seem that both continuous and intermittent systems are active in healthy subjects and dysfunctional in patients with Parkinson's disease but can be improved towards normal with therapy. An interaction between the two control systems could even be speculated, for example failure of the intermittent system in Parkinson's disease leading to compensatory overdrive of the PID system (which reverts to normal levels with therapy). Alternatively, the switching behaviour observed could represent continuous control acting intermittently. However, it could be argued that we directly found evidence only of intermittent switching behaviour in sway and the continuous control system findings simply reflect how the primary dataset aligns to the PID model and does not prove the existence of a continuous control system in neural circuitry. Furthermore, it has been demonstrated mathematically, that an intermittent control system can mimic or improve upon the performance of a continuous control system beset by the type of long and variable feedback delays encountered in the nervous system (Gawthrop *et al.*, 2011; Tanabe *et al.*, 2016).

Thus, the most robust findings from this study relate to the impairment and recovery of switching behaviour detected in sway patterns, interpreted as the impact of intermittent control (but without proving the existence of this model in neural circuitry), with substantial correlations with clinical balance impairment. A possible mechanism for reduced intermittent control in Parkinson's disease, is impaired release of ballistic, pre-programmed motor responses that use reticulospinal pathways (Valls-Solé *et al.*, 1995, 2008; Thevathasan *et al.*, 2011*b*). In patients with Parkinson's disease and severe axial motor impairment, we previously reported that the Start-React phenomenon was absent but restored by PPN DBS, in line with the benefit on gait freezing (Thevathasan *et al.*, 2011*b*). Intermittent adjustments to postural sway, like the responses elicited by Start-React, are considered to be pre-programmed (prepared in advance and ready for automatic release), ballistic (triggered off as a whole) and predominantly use reticulospinal pathways (Gawthrop *et al.*, 2014). The lack of Start-React in Parkinson's disease has since been corroborated by others, and associated with gait freezing but not yet with postural instability (Carlsen *et al.*, 2009*b*; Nonnekes *et al.*, 2014, 2015). In healthy subjects, Start-React has been observed not only in automatic adjustments to gait (e.g. obstacle avoidance and stepping) but also to posture (e.g. leg responses to platform translation) (MacKinnon *et al.*, 2007; Queralt *et al.*, 2008; Nonnekes *et al.*, 2013). Indeed, balance impairment and gait freezing in Parkinson's disease often co-exist, which raises the possibility of shared mechanisms (Giladi *et al.*, 2001*b*; Bekkers *et al.*, 2017). Impairment in the release of relatively small amplitude intermittent adjustments to sway could be considered analogous to the impaired release of larger amplitude responses to a postural challenge, as assessed with the 'pull test' (Munhoz *et al.*, 2004). Indeed, we found a close correlation between intermittent switching of postural sway and clinical balance impairment (combined score for the pull test and arising from a chair). Intermittent switching

of postural sway also correlated with the Parkinson's disease gait subscore, supporting the concept of a partly shared pathophysiology. This proposed 'unblocking' of pre-programmed movement with PPN DBS could be seen as analogous to the improvement in gait observed with external cues and with startling stimuli (Keefe *et al.*, 1989; Glickstein and Stein, 1991; Nieuwboer *et al.*, 2007).

Consistent with the variable results reported in previous studies we found that simple sway parameters of sway area and velocity did not correlate with clinical balance impairment in Parkinson's disease (Horak *et al.*, 1992; Matinolli *et al.*, 2007; Frenklach *et al.*, 2009; Ebersbach and Gunkel, 2011; Johnson *et al.*, 2013). Levodopa and subthalamic nucleus DBS have been reported across studies to have an inconsistent impact on sway area and velocity—although this could well reflect the variable impact of these therapies on balance as well as the confounding effects of dyskinesia (Maurer *et al.*, 2003; Revilla *et al.*, 2013; De la Casa-Fages *et al.*, 2017). We did find that sway area was abnormally large in Parkinson's disease, corroborating a wealth of previous research (Schoneburg *et al.*, 2013). However, PPN DBS did not change sway area despite the improvements observed in clinical balance impairment and control system performance. In this study, sway velocity did not differ between subject groups although a trend suggested that PPN DBS increases sway velocity—from being similar to controls to being increased compared to controls. In the one previous study of the impact of PPN DBS on sway (four patients), a possible albeit modest increase in path length (related to velocity) was also observed (Yousif *et al.*, 2016). That PPN DBS drives sway velocity to abnormally high values could represent worsening of an aspect of sway control or the activation of a compensatory mechanism. The increase in velocity may be related to the increase in switching behaviour as a strong trend suggested a correlation between intermittent switching and sway velocity although the nature of this relationship remains to be established.

The balance control system methods and findings in this study are novel and thus require more extensive investigation to assess their significance in a larger cohort of subjects including Parkinson's disease patients with a broader range of phenotypes. One question is whether sway control system metrics could be useful as biomarkers of balance impairment in Parkinson's disease. PID model parameters correlated with clinical balance impairment but required the additional assessment of reaction time and the assumption that the body conformed to a rigid inverted pendulum. The assessment of intermittent switching of postural sway may therefore be a simpler candidate biomarker; however, further investigation will be needed to assess validity.

Therapeutic potential of PPN DBS

Whilst we found that sway control system metrics returned to normal values with PPN DBS, there was only partial improvement on clinical balance impairment. A partial therapeutic benefit has also been the experience for PPN DBS for gait freezing (Thevathasan *et al.*, 2018). This limited clinical efficacy may reflect that the clinical application of PPN DBS has not yet been optimized or alternatively may reflect a fundamental limitation of the therapeutic mechanism. For example, if all that PPN DBS achieves is a circumscribed unblocking of pre-prepared ballistic motor programmes (such as adjustments to gait and balance), then this may be insufficient for patients in whom other varied systems, such as attentional processing, leads to clinical impairment (Snijders *et al.*, 2016). If so, then one strategy may be to identify patients in whom such blocked ballistic adjustments is the major issue and could therefore benefit most from PPN DBS. Impaired Start-React and reduced intermittent switching of postural sway could be investigated as markers of such reversibility.

There has been much debate regarding the ideal clinical application of PPN DBS, particularly the location of electrodes and stimulation (Hamani *et al.*, 2016*b*). Over time, two PPN regions have been posited; caudal and rostral (Thevathasan *et al.*, 2012*b*; Tattersall *et al.*, 2014). These two regions span a large distance relative to the brainstem, with the rostral PPN proposed as lying 2 mm above and below the pontomesencephalic junction and caudal PPN from 2 mm to 6 mm below the pontomesencephalic junction (Thevathasan *et al.*, 2012*a*). It is reported that alpha band oscillations in local field potentials in the caudal PPN correlated with gait (real and imagined) whereas beta band oscillations in the rostral PPN region did not (Thevathasan *et al.*, 2012*b*; Fraix *et al.*, 2013; Tattersall *et al.*, 2014; Lau *et al.*, 2015). Two studies have offered very preliminary evidence suggesting that caudal PPN DBS may be more effective for gait than rostral PPN DBS (Thevathasan *et al.*, 2012*a*; Fu *et al.*, 2014). In this study, all the patients were stimulated in the caudal PPN (or further below). Within this group, we found no association between stimulation depth and benefit on balance. The question of ideal PPN DBS location would be better addressed in a repeated measures assessment within patients whose electrodes span both rostral and caudal regions. Regardless, it is intriguing that the disparate locations of stimulation applied in this study were capable of yielding a clinical benefit for balance. Some variance in stimulation location is inevitable in clinical practice and reflects both surgical targeting and the contact chosen at the end of the electrode to apply stimulation. In some cases, stimulation locations in this study appear to extend beyond what would typically be considered to be the PPN region (Hamani *et al.*, 2016*a*). This could reflect that stimulation parameters typically used by PPN DBS generate a wide enough field of influence in the compact brainstem to overcome any targeting inconsistencies. Alternatively, the impact of what is termed 'PPN' DBS may actually reflect a fairly non-specific disinhibition of motor responses available in a wide dorsal brainstem region. This recalls a similarly large region where locomotion could be induced in decerebrate animals known historically as the 'mesencephalic locomotor region' (Jenkinson

et al., 2009). However, the current clinical consensus is to accurately target the PPN, ideally with electrode contacts on both rostral and caudal subregions, giving the option to stimulate either (Thevathasan *et al.*, 2018).

Much work is yet needed to see if the clinical application of PPN DBS can be refined to a stage where it is ready to be assessed in a randomized controlled trial evaluating impact on quality of life. However, this study is encouraging that balance impairment in Parkinson's disease may be partly reversible, and may offer mechanistic insights that could assist other emerging therapies.

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Competing interests

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Supplementary material

Supplementary material is available at *Brain* online.

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