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RESEARCH ARTICLE

Cardiovascular autonomic responses in patients with Parkinson disease to pedunculopontine deep brain stimulation

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Abstract

Purpose Dysautonomia can be a debilitating feature of Parkinson disease (PD). Pedunculopontine nucleus (PPN) stimulation may improve gait disorders in PD, and may also result in changes in autonomic performance.

Methods To determine whether pedunculopontine nucleus stimulation improves cardiovascular responses to autonomic challenges of postural tilt and Valsalva manoeuver, eight patients with pedunculopontine nucleus deep brain stimulation were recruited to the study; two were excluded for technical reasons during testing. Participants underwent head up tilt and Valsalva manoeuver with stimulation turned ON and OFF. Continuous blood pressure and ECG waveforms were recorded during these tests. In a single patient, local field potential activity was recorded from the implanted electrode during tilt.

Results The fall in systolic blood pressure after tilt was significantly smaller with stimulation ON (mean − 8.3% versus − 17.2%, $p=0.044$). Valsalva ratio increased with stimulation from median 1.15 OFF to 1.20 ON ($p=0.028$). Baroreflex sensitivity increased during Valsalva compared to rest with stimulation ON versus OFF ($p=0.028$). The increase in baroreflex sensitivity correlated significantly with the mean depth of PPN stimulating electrode contacts. This accounted for 89% of its variance ($r=0.943$, $p=0.005$).

Conclusion PPN stimulation can modulate the cardiovascular system in patients with PD. In this study, it reduced the postural fall in systolic blood pressure during head-up tilt and improved the cardiovascular response during Valsalva, presumably by altering the neural control of baroreflex activation.

Keywords Pedunculopontine nucleus · Deep brain stimulation · Parkinson disease · Postural hypotension · Autonomic nervous system

Introduction

Neurogenic orthostatic hypotension (OH) can be a debilitating feature of synucleinopathies, including Parkinson disease (PD), dementia with Lewy bodies and multiple system atrophy, occurring in 20–50% of PD patients depending on the diagnostic threshold used [1, 2]. It also occurs more rarely in other conditions including diabetic autonomic neuropathy, immune-mediated neuropathies [2] and as a complication of brain tumours involving parts of the central autonomic network in the brainstem [3]. In OH, syncope and dizziness occur due to failure of the sympathetic nervous system to maintain cerebral perfusion pressure upon standing, and there is some evidence that poor cerebral perfusion secondary to OH is also linked to cognitive impairment [4]. Current pharmacological approaches for the treatment of OH can worsen supine/nocturnal hypertension [1], thus exposing patients to alternative risks of cerebral, cardiac and renal disease. Identifying a central target for blood pressure control could provide an option for neuromodulation in cases intractable to contemporary treatment [5].

Neurosurgical implantation of deep brain electrodes for the management of disorders such as PD and chronic pain provides an opportunity to assess the physiological impact of electrical stimulation of focal areas within the human brain [6, 7]. Electrical stimulation at deep brain sites in humans has been found to increase or decrease arterial blood pressure in the range of 14–125 mmHg [5, 8, 9] and improve

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cardiovascular response during postural challenge from sitting to standing [10]. Three case reports have shown improvements in the control of blood pressure following chronic deep brain stimulation (DBS) over two years that resulted in a reduction of antihypertensive medication [9, 11, 12].

Pedunculopontine nucleus (PPN) stimulation is a relatively new therapy in PD that may help with gait and postural instability [13]. The PPN is part of the reticular activating system and is located within the brainstem, straddling the midbrain and pons. It contains within it the mesencephalic locomotor region, stimulation of which has been shown to increase mean arterial blood pressure in animals [14, 15]. The PPN projects dense cholinergic connections to the rostral ventrolateral medulla [16], a site regarded as a key central regulator of arterial blood pressure [17, 18]. Chemical activation of the PPN in anesthetised rats produces elevations in sympathetic nerve activity, blood pressure and baroreflex, as well as muscle activity [19]. Here we investigate whether stimulation of the PPN in awake humans influences arterial blood pressure during the postural challenge of head-up tilt and Valsalva manoeuver.

Methods

Patients

Patients receiving chronic bilateral PPN stimulation for PD (meeting UK Brain Bank criteria) were recruited from centers in Oxford, UK, and Brisbane, Australia. DBS was not inserted as part of a clinical trial. Ethical approval was obtained from both centers in addition to written informed consent. The study conformed to the Declaration of Helsinki and local institutional guidelines. Indications for this treatment and implantation technique have been reviewed elsewhere [20]. Patients receiving antihypertensive medication were excluded. Testing was performed in the antiparkinsonian medication 'ON' state. Stimulation used a bipolar configuration with mean amplitude 2.9 volts (range 2.2–4.3 volts), mean frequency 30 Hz (range 20–35 Hz) and all used a 60 μs pulse width. Only therapeutically relevant contacts and stimulation parameters were used. One patient (patient 2) had STN electrodes, which were OFF throughout the experiment.

Experiment 1: Tilt-table testing

Patients were tested in a quiet, thermostatically-controlled room (26 °C). Patients lay supine on a tilt table for 10 min. Head-up tilt (HUT) then occurred over 10 s–80°. Data were recorded for 3 min immediately before HUT, and 3 min immediately after HUT. This experiment was repeated for two conditions, ON and OFF therapeutic bilateral PPN stimulation. The order of conditions was randomised, with a 10 min washout period enforced after changing stimulation, so that minimal change in medication state occurred between tests. Patients did not receive medication between tilts. Patients were blinded to condition and experiment hypotheses.

Experiment 2: Valsalva manoeuver

Patients were tested with stimulation ON and OFF (as with HUT), however the order of stimulation was reversed compared to the tilt testing. This measure reduced the likelihood that any differences in outcome between the ON and OFF conditions were explained simply by a test order effect. Patients sat comfortably in a chair at rest. Expiration was then performed via a 20 ml syringe barrel against a manometer to achieve a pressure of 20–40 mmHg, sustained for 15 s, as per Mathias and Bannister [21].

Recordings

Blood pressure waveforms were recorded with a continuous, non-invasive plethysmograph (Finapres Medical Systems, Amsterdam, Netherlands) with a finger cuff. The arm was positioned by the patient's side with height correction by fluid column. The single observer had undergone training and performed in an autonomic testing laboratory in the UK for over 12 months. A 3-lead electrocardiogram (ECG) recorded heart rate and rhythm. Local field potentials (LFPs) for a single patient (patient 5) in the stimulation OFF phase of the trial were recorded from PPN via externalized DBS electrodes. Recording was not possible in the stimulation ON condition. Bipolar LFPs were recorded from three adjacent pairs of deep brain electrode contacts (contacts 0–1, 1–2, and 2–3) with a common electrode placed on the surface of the mastoid, amplified (×10,000, Cambridge Electronic Design, Cambridge, UK), bandpass-filtered at 0.5–500 Hz, and digitized using CED 1401 mark II at a sampling rate of 2000 Hz, displayed on-line and saved onto a hard disk using a custom-written program in Spike2 (Cambridge Electronic Design, Cambridge, UK). All signals were recorded in Spike II software (version 5, Cambridge Electronic Design).

Data reduction and analysis

Signals analysis was performed using MATLAB (version 6.1, Mathworks Inc., Natick, MA). Plethysmograph yielded parameters of systolic (SBP), diastolic blood pressure (DBP) and pulse pressure (PP, the difference between SBP and DBP). Analysis of the maximum blood pressure waveform gradient (dP/dt—the differential of pressure against time), yielded a surrogate measure of cardiac contractility

[22]. ECG yielded heart rate and RR interval. Baroreceptor sensitivity (BRS) was calculated from the transfer function of the SBP and RR interval using bivariate autoregressive modeling [23].

The primary outcome measure in Experiment 1 (tilt) was assigned as percentage change in SBP after HUT. This was calculated from the mean baseline supine SBP compared to the mean SBP during the 3 min of HUT.

The primary and secondary outcome measures in Experiment 2 were Valsalva ratio (VR) and BRS, respectively. VR was calculated as the ratio between the fastest heart rate during Phase II and the slowest heart rate of Phase IV of the Valsalva manoeuvre as per Goldstein 2003 [1]. Normal VR is considered to be ≥ 1.21 and has been demonstrated to be diminished in PD [1]. BRS has also been shown to be diminished in patients with PD, and linked to OH [24]. The percentage change in BRS between rest and Valsalva manoeuvre was recorded and compared between ON and OFF PPN DBS conditions. HRV and blood pressure variability (BPV) were derived by autoregression of RRI and systolic blood pressure trace, respectively, and decomposed into low frequency (LF 0.04–0.15 Hz) high frequency (HF 0.15–0.4 Hz) and LF:HF ratio. The single-subject time–frequency representation of LFPs was estimated using short-time Fourier transform (STFT) method with 1 s of Hanning window and 0.5 s overlap. The power spectral density (PSD) were calculated using the Welch periodogram method with a 1 s of Hanning window and 0.5 s overlap.

Statistical analysis

The Kolmogorov–Smirnov Test demonstrated that blood pressure data were normally distributed. Accordingly, paired *t* tests were applied to compare parameters between stimulation conditions. BRS was not normally distributed so the Wilcoxon signed-rank test was used for this parameter. All tests were two tailed. *P* values < 0.05 after correction for multiple comparisons were considered significant (3). Data were analysed using the Statistical Package for Social Sciences (SPSS version 11, SPSS Inc., Chicago, IL). The Benjamini and Hochberg method of correcting for multiple comparisons was used.

Results

Six patients were studied, four males and two females. All patients had had PPN DBS electrodes inserted for treatment of movement disorder symptoms in PD and were not part of a major clinical trial. Blood pressure waveform could not be transduced in one patient due to excessive digital artery constriction and another could not perform the Valsalva manoeuver competently; as a result these subjects were excluded. Mean age was 60.3 years (range 46–72 years), mean PD duration was 15.7 years (range 10–20 years), mean time since surgery for PPN DBS electrode implantation was 44.5 months (range 12–58 months). No patient had a previous diagnosis of orthostatic hypotension. See Table 1 for patient descriptions and Tables 2, 3 for results summary.

Table 2 % change in systolic blood pressure after tilt with DBS ON and OFF, for individual patients

Patient	% change in systolic blood pressure after tilt (DBS ON)	% change in systolic blood pressure after tilt (DBS OFF)
1	− 19.43	− 32.1
2	− 0.51	1.69
3	− 14.70	− 21.1
4	− 10.06	− 15.55
5	1.20	− 20.11
6	− 2.95	− 10.11

Table 1 Summary of patients' characteristics

Patient	Age/sex	PD duration (years)	Post-op duration (year, months)	L-Dopa equivalent dose (mg/day)	UPDRS III OFF/ON meds	FOGQ pre/postop	FallsQ pre/postop
1	72/M	18	2, 5	2500	25/17	14/11	4/2
2	46/M	20	2	Nil (STN DBS in-situ)	68/34	*n*/14	*n*/4
3	61/F	10	2	800	40/23	24/16	4/3
4	72/F	10	2	950	38/22	22/13	4/2
5	55/M	20	1	850	51/19	14/15	4/4
6	56/M	16	2, 10	1400	43/16	23/17	4/4

PD parkinson disease, *UPDRS* unified Parkinson disease rating scale, *FOG* freezing of gait questionnaire, *Q* questionnaire

Table 3 Summary of primary, secondary and other variables measured during experiment 1 (head-up tilt)

Stimulation	Systolic blood pressure (mmHg) Mean ± SE	dP/dt (mmHg/s) Mean ± SE	Pulse pressure (mmHg) Mean ± SE	Baroreceptor sensitivity (ms/mmHg) Mean ± SE	Diastolic blood pressure (mmHg) Mean ± SE	Heart rate (beats per min) Mean ± SE
ON						
Pre-tilt	122.1 (± 15.6)	5491.8 (± 755.0)	37.2 (± 4.9)	10.9 (± 3.4)	84.8 (± 19.1)	76.9 (± 5.5)
Post-tilt	114.1 (± 18.2)	4681.7 (± 836.0)	31.3 (± 5.9)	7.4 (± 2.1)	83.0 (± 22.1)	84.8 (± 6.6)
OFF						
Pre-tilt	109.7 (± 6.8)	6770.3 (± 358.2)	43.4 (± 2.9)	6.6 (± 1.0)	66.2 (± 8.1)	76.6 (± 4.2)
Post-tilt	92.0 (± 10.1)	4923.9 (± 615.7)	32.2 (± 4.7)	9.6 (± 2.2)	59.8 (± 10.6)	85.1 (± 5.8)
	(%) Mean ± SE	(%) Mean ± SE	(%) Mean ± SE	(ms/mmHg) Mean ± SE	(%) Mean ± SE	(%) Mean ± SE
ON						
Change with tilt	− 8.3 (± 3.4)	− 18.2 (± 5.6)	− 20.6 (± 8.0)	− 3.5 (± 3.0)	− 6.9 (± 4.6)	10.1 (± 3.2)
OFF						
Change with tilt	− 17.2 (± 4.6)	− 28.1 (± 5.7)	− 27.3 (± 7.2)	3.0 (± 1.5)	− 12.7 (± 6.2)	10.8 (± 3.4)
t/z, df	2.679, 5	4.107, 5	3.649, 5	− 1.992, 5	–	–
p value	0.044*	0.018*	0.030*	0.046*	–	–

*Indicates statistical significance

Experiment 1: Tilt

Blood pressure parameters

PPN DBS significantly reduced the postural drop in SBP with HUT: the percentage change in mean SBP after HUT with stimulation was − 8.3% (SE ± 3.4%), significantly smaller than the change of − 17.2% (SE ± 4.6%) without stimulation, $p = 0.044$ (Fig. 2). Three patients (#1, #4, #5) had a postural SBP fall of > 20 mmHg (28.6, 22.8, 26.5 mmHg, respectively) when the stimulator was OFF, consistent with orthostatic hypotension. With PPN stimulation, the postural SBP fall was no longer consistent with orthostatic hypotension in any of these three patients; the magnitude of the drop was no longer within the orthostatic hypotension range for patients one and four (18.7, 13 mmHg, respectively), and mean SBP increased after HUT (− 2.1 mmHg) in patient five. See Table 2 for SBP values following tilt with DBS ON and OFF for individual patients.

The only non-responder, patient #2, had permanantly deactivated bilateral STN electrodes although the relevance of this is unknown. STN DBS was no longer providing any clinical benefit for the patient, but it is known that STN DBS has positive effects on cardiovascular dysautonomia and it is possible that there was a long-term carry over effect from STN stimulation.

The decrement in dP/dt with HUT was less in the 'stimulation ON' than 'stimulation OFF' condition (percentage change − 18.2% versus − 28.1%, $t = 4.107$, $df = 5$, $p = 0.018$). Pulse pressure also fell less in the 'stimulation ON' than 'stimulation OFF' condition (mean change − 20.6% versus − 27.3%, $t = 3.649$, $df = 5$, $p = 0.030$). Figure 1(a) demonstrates cardiovascular variables changing in an illustrative patient with stimulation ON and OFF.

Arterial baroreceptor reflex

BRS was higher whilst supine with stimulation turned ON compared to OFF (mean BRS 10.9 ms/mmHg ON stimulation versus 6.6 ms/mmHg OFF stimulation).

Stimulation significantly reduced BRS during HUT whereas BRS increased during HUT in the OFF stimulation state (mean BRS change − 3.45 versus + 3.02 ms/mmHg, $z = -1.992$, $df = 5$, $p = 0.046$).

Repeated measures

As part of quality control, five patients were retested several months later. The HUT protocol described above was repeated with PPN stimulation ON and OFF, in the reverse order to their original testing. All participants except subject 2 demonstrated superior cardiovascular response to HUT with stimulation ON.

Experiment 2: Valsalva

Cardiovascular response to Valsalva manoeuver improved with stimulation compared to without (see Fig. 1b, c).

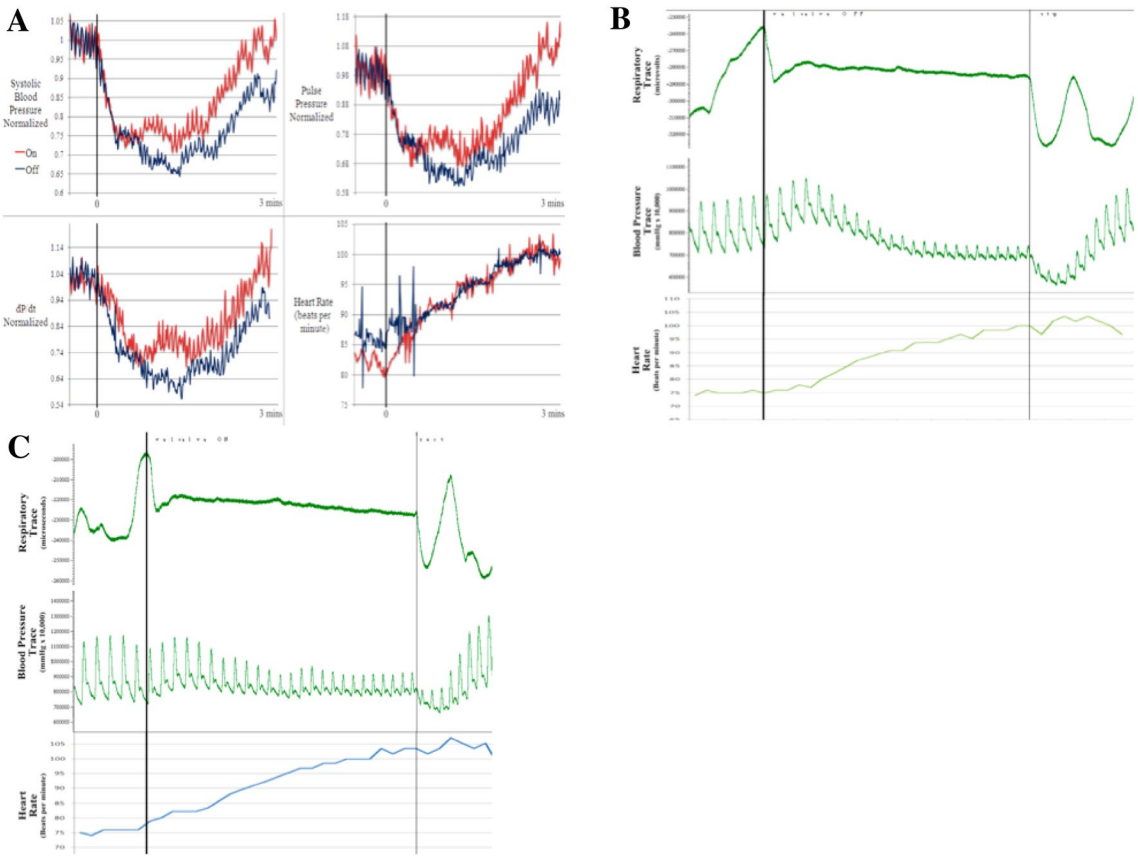

Fig. 1 **a** Graphs to show difference in cardiovascular variables after head-up tilt (vertical black line) with stimulation ON and OFF in a representative patient. Normalization was performed against mean pre-tilt baseline values. Arterial blood pressure parameters fell less with stimulation ON and recovered to pre-tilt levels or higher, unlike in the OFF state. **b** Valsalva manoeuvre performed without stimulation in a representative patient. Black line depicts the beginning of manoeuvre, grey line depicts end of manoeuvre after 15 s. A trailing-off in the magnitude of the blood pressure trace is seen, characteristic of the dysautonomic response in Parkinson disease. **c** Valsalva manoeuver performed with stimulation in the same representative patient. Black line depicts the beginning of manoeuvre, grey line depicts end of manoeuvre after 15 s. Pulse pressure narrows less and systolic and diastolic blood pressure are better maintained than without stimulation. The characteristic dysautonomic trailing-off of blood pressure in Parkinson disease and without stimulation is not seen here with stimulation. Heart rate increases earlier and to a greater magnitude with stimulation

Valsalva ratio

The median Valsalva ratio (VR) OFF PPN DBS was 1.15 (SE ± 0.06), demonstrating a baseline tendency to a dysautonomic response in the patient group. VR increased towards normal with PPN DBS turned ON, improving to 1.20 (SE ± 0.06) (supplementary data, Table 1). The Valsalva ratio improvement with PPN DBS was 5.0% (median improvement), (SE ± 1.5%, range 0.34–8.51%). There was only a small, non-significant correlation between % VR improvement and mean contact depth relative to the pontomesencephalic (PM) junction (Spearman's rho = 0.257, $n = 6$, $p = 0.623$).

BRS increased significantly during Valsalva compared to rest with stimulation ON versus OFF ($z = -2.201$, $p = 0.28$). BRS increase did appear to correlate with mean depth of stimulating electrode contacts relative to the PM line, whereby it explained 89% of its variance (Spearman's rho = 0.943, $n = 6$, $p = 0.005$). A single outlier that may have skewed this correlation was removed but after re-calculation the relationship was still very strong (rho = 0.900, $n = 5$, $p = 0.037$) (see Fig. 2).

Heart rate variability and blood pressure variability

BPV data, but not HRV data, were normally distributed. Accordingly, medians are presented for HRV data and means for BPV data. Large changes were seen in all components of HRV and BPV. LF HRV increased from a median of 983–1854 ms^2/Hz with stimulation, whilst HF HRV decreased from 219 to 89 ms^2/Hz. This conferred an increase in LF:HF ratio from 264 to 634, suggesting a greater sympathetic activity during Valsalva manoeuvre with stimulation.

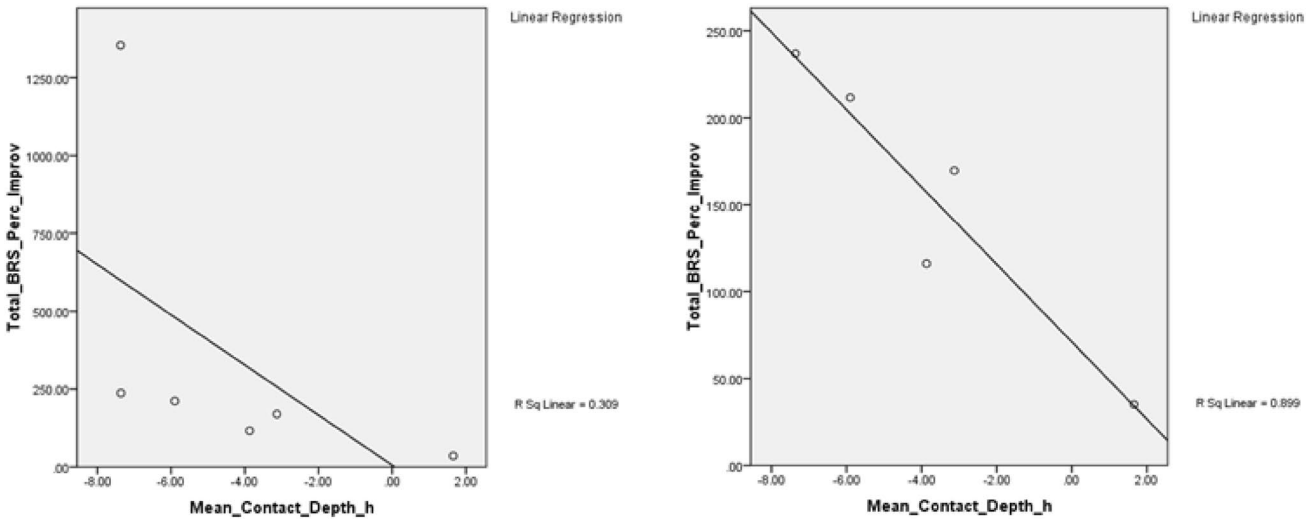

Fig. 2 Correlations of Baroreceptor sensitivity percentage improvement with stimulation versus mean depth of electrode contacts **a** including outlier; and **b** with outlier removed

However, none of the changes in these indices reached statistical significance using Student's paired samples *t* tests.

Correlation between cardiovascular parameters and motor scores

We compared all changes in cardiovascular parameters between stimulation ON and OFF with changes in motor scores (% improvement in freezing of Gait score and Falls). Analysis using Spearman's correlation did not reveal any significant correlations ($p > 0.05$ for all analyses). The data were tested with and without patient 2 as an outlier. (Data not shown).

Local field potentials

We investigated the effect of HUT on PPN oscillatory activity in patient 5, depicted using time–frequency representation of the LFPs (Fig. 3). The spectrogram exhibited predominately low frequency oscillations (<2 Hz) and alpha oscillations (8–15 Hz) before HUT. Following HUT, the

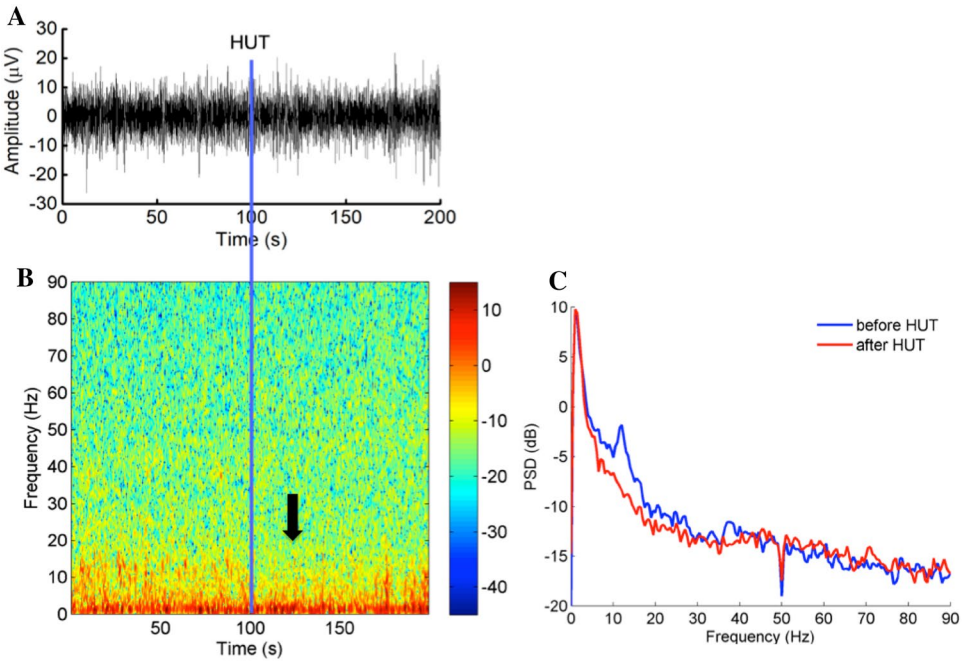

Fig. 3 Local field potential trace (**a**) and time–frequency representation (**b**) recorded from PPN in a single subject before and after HUT (solid line indicates time of HUT). Vertical arrow indicates reduction in alpha band power (8–12 Hz) following HUT. **c** Power spectral density before and after HUT demonstrating reduced power after HUT at around 10 Hz

power of alpha oscillations in PPN decreased notably, from an average power of − 4.1 dB before tilt to − 7.9 dB after tilt.

Discussion

This study has identified cardiovascular effects of PPN stimulation in awake humans. PPN stimulation limited the postural fall in arterial SBP after HUT in patients with PD. Although there was an initial drop in systolic blood pressure following tilt with PPN stimulation ON and OFF, by 3 min following tilt, there was a significant recovery in blood pressure in the stimulation ON group compared with the stimulation OFF group. In three patients whose SBP fall (OFF stimulation) was large enough to meet the criteria for postural hypotension, PPN stimulation corrected the extent of this fall such that they were no longer within that diagnostic category. Furthermore, the pathological cardiovascular response to Valsalva manoeuvre was shifted towards the normal state. It is unclear if these effects may be beneficial for patients with symptomatic postural hypotension, and our findings require confirmation in a larger series of patients, ideally with established dysautonomia.

The secondary variables suggest the mechanisms by which these blood pressure effects were mediated. PPN stimulation produced better maintenance of pulse pressure and dP/dt after HUT. As markers of peripheral vascular tone and myocardial contractility, respectively, this suggests that the SBP effects of PPN stimulation were mediated via both peripheral and central components of the cardiovascular system. As dP/dt and pulse pressure are only surrogate markers of contractility and peripheral vascular resistance, respectively, we can only speculate upon this. However, the results suggest that arterial blood pressure was not being modulated by chronotropic responses, as heart rate increases after tilt were equivalent with or without stimulation. DBS of the periaqueductal grey area of the midbrain has been shown to modulate peripheral autonomic variables, including muscle sympathetic nerve activity (MSNA) [7] and peripheral vascular resistance [6], illustrating that central neuromodulation can effect peripheral changes.

The reduction in BRS with PPN stimulation after HUT suggests that the maintenance of SBP was facilitated by a descending interference with the baroreceptor reflex arc, reducing its sensitivity to changes in arterial blood pressure, which would otherwise trigger vagal activation and sympathetic inhibition via the nucleus tractus solitarius. It should be noted that the resting arterial pressure was higher pre-tilt in the stimulation ON group compared to the OFF group. Increased BRS at rest is also seen with periaqueductal grey (PAG) stimulation that has been shown to resist postural arterial blood pressure fall on standing. Whilst it is possible that an increased resting sympathetic tone may be part of the explanation for the reduced postural drop, and increased cardiovascular response during Valsalva, the increased resting BRS and reduction after HUT in the ON group (compared to an increase after HUT in the OFF group) would tend to mitigate against this being the only explanation. The single-subject local field potential data also support the view that HUT specifically induces neural changes in PPN oscillatory activity at the time of tilt itself.

Sverrisdottir et al. found that PAG DBS could alter BRS and MSNA depending on the site of the stimulation [7]. Ventrolateral PAG stimulation reduced BRS with a simultaneous decrease in arterial blood pressure and HR. MSNA burst frequency and intensity also reduced in parallel. They also studied one patient with bilateral PPN electrodes and found no change in BRS, nor MSNA burst frequency, burst amplitude distribution, or burst incidence recorded from the common peroneal nerve and did not find a significant improvement in sBP with stimulation.

Patient #2 did not respond and was the only patient who was not naïve to DBS. This patient had originally been treated with bilateral subthalamic nucleus (STN) stimulators for rigidity but had suffered a decline in gait and postural stability prompting the subsequent bilateral PPN implantation. The patient was tested with STN stimulators OFF and PPN stimulators both ON and OFF. STN stimulation was demonstrated by Stemper et al. to improve orthostatic regulation in patients with Parkinson disease [25]. Compared to the OFF stimulation state, STN stimulation led to an increase in heart rate, maintenance of arterial blood pressure, reduction in skin blood flow and maintenance of baroreceptor sensitivity after 60° head-up tilt testing (HUT). This contradicts other HUT investigations that found no effect from STN stimulation in PD patients on markers of autonomic function [8, 26], although Thornton et al. first demonstrated in humans that STN DBS could increase arterial blood pressure and HR at rest, which was associated with facilitated movement [27]. We can only speculate upon why PPN stimulation did not facilitate a superior cardiovascular response in this patient.

The PPN may be causing the cardiovascular effects described here directly via the rostral ventrolateral medulla to which it sends projections [16] or via connections to other centers implicated in blood pressure control.

In PD, BRS during Valsalva is abnormally reduced [1]. Further, the surge in heart rate to compensate for the reduction in venous return due to the increased intrathoracic pressure is greatly diminished and is expressed as a reduction in Valsalva ratio below 1.21. With stimulation, both BRS was increased and median VR was improved towards normal from 1.15 to 1.20. The changes in HRV and BPV suggest that an increase in sympathetic activity is produced with stimulation during Valsalva to compensate for the fall in venous return, whereby both LF:HF ratios increased. Abnormalities in HRV and BPV are associated with serious

cardiovascular pathologies including myocardial infarction and stroke [28, 29]. The fact that these could be altered by DBS is exciting although it should be borne in mind that neither parameter reached statistical significance when adjustment for multiple variables was taken into account. Had there been more patients studied, one could speculate that HRV and BPV changes may have been significant. Testing a large number of patients receiving PPN stimulation is very challenging, as the numbers who have undergone this surgery worldwide is still only within double figures, as the narrow indications for the surgery make it uncommon.

The results of this study support the conclusion that PPN stimulation appears to rectify the dysautonomic response seen during autonomic challenge in PD. The MLR, of which the PPN is a component, elevates arterial blood pressure, even after muscle paralysis when electrically stimulated in decerebrate or anaesthetised animals [14]. A possible confound would be that PPN stimulation improves venous return secondary to an increase in muscle tone but it is noteworthy that PPN stimulation did not evoke any muscle contractions or somatomotor sensations in our patients. An alternative hypothesis, given the intimacy of the PPN with the parabrachial nuclei throughout most of its length, the locus coeruleus caudally, or the cerebellum via white matter projections as demonstrated in tractography studies [30, 31] is that cardiovascular effects are mediated through activation of these components of the central autonomic network [32]. The more caudal the stimulation, the greater the improvement in BRS during Valsalva manoeuvre, reaching a Spearman's rho of 0.90. This may relate to the properties of the caudal PPN itself or that the stimulation is reaching related structures, the most likely candidate being the locus coeruleus. To investigate these effects further, testing at different contacts (rostral–caudal) and at different voltages would be a useful next line of investigation.

There are certain limitations of the study. One such limitation, which limits the strength of the conclusions we are able to draw, is the small "*N*" number, a result of the relatively low number of patients implanted with PPN DBS and the resulting small pool from which to recruit. Moreover, a potential confound needs consideration—that differences in dopaminergic medication state could have influenced the results. However this is unlikely, given that the entire HUT experiment took only 26 min, during which time variance of dopaminergic state would be only modest. Additionally, the order of stimulation conditions was randomised and then also reversed between tilt and Valsalva manoeuver. Despite these order randomizations and reversals, stimulation produced superior performance compared to the OFF state. Furthermore, when we looked for any correlation between motor effects and cardiovascular effects, there were no significant correlations, suggesting that these changes do not represent an improvement in motor function per se.

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Author contributions Conception of project: JAH, ALG, DJP, TZA. Study design: JAH, ALG, DJP, GK, PS. Data collection: JAH, JSB, SW, NFAB, JR, IS. Insertion of DBS electrodes: ALG, TZA, TC. Analysis and manuscript composition: JAH, HAR, YH, ALG, GK. Manuscript feedback: all authors

Compliance with ethical standards

Conflict of interest JA Hyam, TJ Coyne, TZ Aziz and AL Green have received honoraria from Medtronic Inc. and St. Jude Medical. No author is employed or has investment in either company. Prof Green is on an Executive Advisory Board (Movement Disorders) for Abbott and holds a consultancy agreement with Abbott. He also has a Consultancy agreement with Renishaw plc. He has given Expert testimony (unrelated) and receives Royalties from Oxford University Press (unrelated). He holds an MRC grant (unrelated to this project).

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