Effects of Deep Brain Stimulation on postural control in Parkinson's disease

Mitesh Patel [*, #, 1,2], **Maria H. Nilsson** [*, 3,4,5], **Stig Rehncrona** [6], **Fredrik Tjernström** [7], **Måns Magnusson** [7], **Rolf Johansson** [8], **Per-Anders Fransson** [7]

[1] Division of Brain Sciences, Imperial College London, W6 8RF London, UK

[2] Faculty of Science and Engineering, School of Medicine and Clinical Practice, University of Wolverhampton, Wolverhampton, WV1 1LY, UK.

[3] Department of Health Sciences, Lund University, S-221 85 Lund, Sweden

[4] Memory Clinic, Skåne University Hospital, S-212 24 Malmö, Sweden

[5] Clinical Memory Research Unit, Faculty of Medicine, Lund University, S-221 85 Lund, Sweden

[6] Department of Neurosurgery, Lund University, S-221 85 Lund, Sweden.

[7] Department of Clinical Sciences, Lund University, S-221 85 Lund, Sweden.

[8] Department of Automatic Control, Lund University, S-221 00 Lund, Sweden

*These authors contributed equally.

Corresponding author

[#] **Mitesh Patel**

Abstract

The standard approach to the evaluation of tremor and stability control in medical practice is subjective scoring. The objective of this study was to show that signal processing of physiological data, that are known to be altered by tremor and other cardinal symptoms in Parkinson's disease (PD), can quantify the postural dynamics of this disease and the effects of DBS technology. We measured postural control and its capacity to adapt to balance perturbations with a force platform and perturbed balance by altering visual feedback and using pseudo-random binary sequence perturbations (PRBS) of different durations. Our signal processing involved converting the postural control data into spectral power with Fast-Fourier Transformation across a wide bandwidth and then subdividing this into three bands (0-4Hz, 4-7Hz and 7-25Hz). We quantified the amount of power in each bandwidth.

From 25 eligible participants, 10 PD participants (9 males, mean age 63.8 years) fulfilled the inclusion criteria; idiopathic PD responsive to L-Dopa; >1 year use of bilateral STN stimulation. Seventeen controls (9 males, mean age 71.2 years) were studied for comparison. Participants with PD were assessed after overnight withdrawal of anti-PD medications. Postural control was measured with a force platform during quiet stance (35seconds) and during PRBS calf muscle vibration that perturbed stance (200seconds). Tests were performed with eyes open and eyes closed and with DBS ON and DBS OFF. The balance perturbation period was divided into five sequential 35-second periods to assess the subject's ability to address postural imbalance using adaptation.

The signal processing analyses revealed that activating the DBS device did not significantly change the dynamics of postural control in the 0–4Hz spectral power

but the device reduced the use of spectral power >4Hz; a finding that was present in both anteroposterior and lateral directions, during vibration, and more so in eyes open tests. Visual feedback, which usually improves postural stability, was less effective in participants with PD with DBS OFF across all postural sway frequencies during quiet stance and during balance perturbations. The expected adaptation of postural control was found in healthy participants between the first and last balance perturbation period. However, adaptation was almost abolished across all spectral frequencies in both the anteroposterior and lateral directions, with both eyes open and eyes closed and DBS ON and OFF in participants with PD.

To conclude, this study revealed that the DBS technology altered the spectral frequency dynamics of postural control in participants through a reduction of the power used >4Hz. Moreover, the DBS device tended to increase the stabilizing effect of vision across all spectral bands. However, the signal processing analyses also revealed that DBS was not able to restore the adaptive motor control abilities in PD.

Key Words: Parkinson's disease; postural control; Spectral analysis

Introduction

In Parkinson's disease (PD) an insufficient formation and action of dopamine in the substantia nigra pars compacta causes defective transmission of impulses from the basal ganglia [1, 2]. This results in defective motor control, bradykinesia, rigidity, tremor and postural instability. Although postural instability and tremor are often present simultaneously, dramatic reductions of tremor amplitude - through Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) – do not always improve

postural stability in PD [3-6]. However, other studies have reported that individuals with PD experience tremor-related fluctuations to standing balance [7-9]. Moreover, with levodopa treatment or DBS of the STN (DBS STN), and even more so with combined treatment, tremor oscillations vanish and sway becomes slower [10]. The discrepancy between these findings deserves further investigation as they may be related to frequency specific components of the postural sway, which can be explored through signal processing using spectral analysis. Spectral analysis has shown that individuals with PD express increased power in sway above 1Hz compared to controls but reduced power in sway below 0.7Hz [11], suggesting a frequency-dependent effect. However, these authors did not quantify the size of spectral power using signal analysis nor did they explore the effect of tremor. Instead, they aimed to study the coherence between spectral frequency of sway and the amplitude of sway. Establishing a computerized approach to the quantification of postural dynamics in patients with tremor is crucial because the current method of assessing this is by subjective scoring (using measures such as the Unified Parkinson's Disease Rating Scale).

A method of exploring defects of postural control by using quantitative objective methods is to perturb upright postural stability through proprioceptive skeletal muscle vibration of the lower leg. Balance perturbations are commonly used in posturography tests, as the increased postural challenge enhances the ability to reveal pathologies and to analyze the contribution from vision for postural control [12-14]. Bilateral muscle vibration over the gastrocnemii results in a vibratory-induced stretch reflex that causes a posterior displacement. This displacement is the result of increased activation of muscle spindles, which produces illusory muscle lengthening. Corrective mechanisms produce an anterior displacement when the vibration stops.

When vibration is applied repeatedly, with on-off durations determined by a pseudorandom binary sequence [15,16], the balance perturbations normally result in postural adaptation, which diminishes the amplitude of anterior and posterior displacement. Postural adaptation is a form of motor learning and recent work suggests that the adaptation process is weaker in PD during repeated platform perturbations than healthy controls [17].

In addition to proprioception, the maintenance of postural control is dependent on visual information. However, visual disorders are common in PD, which presents a particular challenge for fall prevention [18, 19]. Understanding the contribution of visual information to postural control in PD is therefore important. Previous research has indicated that patients with PD are more dependent on visual feedback, meaning that they rely more on visual cues for postural control compared to controls [20, 21]. An important question is therefore whether the contribution of vision is associated with the spectral contents of postural sway and is altered by DBS STN or during postural adaptation.

Presently, one of the most effective treatments for tremor is DBS STN technology [22]. DBS STN significantly reduces parkinsonian postural tremor amplitude [3, 23] and the need for anti-PD medication, thus reducing motor complications from dopamine therapy [24]. Our previous work has showed no significant difference in torque variance (a measure of energy used) between DBS ON and DBS OFF in participants with PD, which is perhaps surprising given the reduction of tremor in the DBS ON state [3]. However, based on the findings of Matsuda and colleagues showing a frequency dependent effect on regular postural sway in patients with PD [11], we suspected and hypothesized that low frequency postural sway is unaffected by DBS but high frequency sway is reduced. However, the spectral composition of

postural sway across a broad frequency range (i.e., the postural dynamics) in individuals with PD is yet to be explored in terms of the contribution played by treatment (DBS), by vision (eyes closed) and during postural adaptation to repeated balance perturbations (gastrocnemii vibration).

Our aim was to conduct a signal processing analysis of torque under quiet and perturbed standing from bilateral vibration over the gastrocnemii (calves), with eyes open and eyes closed, in participants with PD who have DBS STN. Thus, in this study, we used spectrum analysis to quantify the dynamics of postural sway in PD, whether the DBS technology can restore postural dynamics and adaptation. We studied adaptation, as this feature of motor learning is required to address postural challenges, and whether there were alterations to the contribution from vision [13, 14]. Typically, a number of vital neurological properties such as characteristics of motor control plasticity are difficult to discern in the standard quiet stance posturography tests or with the Unified Parkinson's disease Rating Scale (UPDRS) assessments. Hence, the average spectral power was calculated for three frequency bandwidths: 0-4Hz, 4-7Hz and 7-25Hz. These bands were selected as the 4-7Hz band is mainly affected by PD resting tremor [25] and the 7-25Hz band by postural 'action' tremor and harmonic activity [26]. The 0-4Hz lower frequency band corresponds to stability control and slower alterations of movement [27-30].

Materials and methods

Ethical approval

The experiments were performed in accordance with the Helsinki declaration and all patients gave written informed consent. The study was approved by the Regional Ethics Review Board in Lund (411/2006), Lund University, Lund, Sweden. The

ethical approval included the procedure of overnight withdrawal of anti-PD medications, which is a common procedure also in regular clinical practice, i.e. when assessing Levodopa responsiveness and/or when selecting candidates for surgical treatment; it can also be done for evaluating the effects of DBS [31].

Participants

At the time of recruitment, 25 individuals were eligible (22 men, three women) according to the inclusion criteria: idiopathic PD responsive to L-Dopa, between 50-70 years old and having had bilateral STN stimulation for at least one year, to ensure stable DBS treatment. One patient declined participation, and 14 participants were excluded due to the following exclusion criteria: concomitant diseases interfering with balance testing (e.g. known loss of sensibility in the lower extremities, severe comorbidity/pain), an inability to cooperate or an inability to stand for two minutes without support. Ten individuals with PD participated in the study (9 males, mean age 64.3 years (SD 4.0 years, range 59-69 years)). Descriptive information (e.g. L-dopa equivalents and DBS parameter settings) is provided in Table 1. The neurosurgical procedure has been described elsewhere [32]. For comparison, each individual patient was concomitantly scored with the Unified Parkinson's disease Rating Scale (UPDRS) in DBS ON and DBS OFF by the same expert (specialist PD nurse or Neurologist), while this expert was blinded to the DBS state. All patients were recruited from the Department of Neurosurgery, Skåne University Hospital.

A control group comprised 17 participants (9 males, mean age 71.2 years (SD 4.1years, range 65 -79 years)) with no history of falls or neurological/musculoskeletal conditions.

Table 1. Patient characteristics

Patients' characteristics		**Median (range)**
Gender		9 men, 1 woman
Age (years)		65 (59-69)
Duration of disease (years)		18 (10-22)
L-dopa equivalent dose (mg/day)		416 (294-989)
Duration of DBS treatment (months)		37 (15-70)
DBS parameter settings	Right: - Amplitude (V)	3.3 (2.5 - 4.3)
	- Pulse width (μs),	60 (60 - 90)
	- Frequency (Hz)	145 (100 - 185)
	Left: - Amplitude (V)	3.4 (2.2 - 4.3)
	- Pulse width (μs),	60 (60 - 90)
	- Frequency (Hz)	130 (100 - 185)
Location of contacts with negative polarity in relation to the midpoint of the intercommissural line	Right (mm): - Lateral	11.7 (10.4 - 13.1)
	- Posterior	3.4 (3.0 - 4.0)
	- Inferior	2.1 (1.0 - 5.6)
	Left (mm): - Lateral	11.4 (9.6 - 13.0)
	- Posterior	3.5 (3.3 - 5.2)
	- Inferior	2.6 (1.2 - 4.2)
	Intercommissural line (mm)	24.8 (23.5 - 25.6)
UPDRS part III scores, without anti-PD medication		
- DBS turned OFF	Item 20 & 21 (tremor)	2.3 (0 - 8.1)
	Total Score	41.0 (35.0 - 83.5)
- DBS turned ON	Item 20 & 21 (tremor)	0 (0 – 0)
	Total Score	21.5 (11.0 - 30.5)

- Levodopa equivalent doses calculated according to Østergaard et al. [33], and Calne [34].
- UPDRS part III: Unified Parkinson's disease Rating Scale, motor examination. The maximum total score on the UPDRS part III is 108 points, and higher scores reflect more severe motor symptoms.
- Without medication: Overnight withdrawal of all anti-Parkinsonian medication for 10-12 hours. All individuals were on L-dopa, and seven out of the ten participants were on dopamine agonists (ranging from 20-50% of L-dopa equivalent dose). When tested, all participants experienced clinical off symptoms.
- The UPDRS assessments were done at the same occasion as the physical assessments of tremor.

Procedure

In participants with PD, all anti-PD medications were withdrawn the night before testing (from 10pm) and all were kept as in-patients. The following morning an independent healthcare professional programmed the DBS to deliver stimulation (ON) or not (OFF). The order of DBS ON/OFF and posturography with eyes closed (EC) and eyes open (EO) were randomized by placing test order codes in unmarked envelopes to avoid systematic differences and bias. The DBS settings were concealed to personnel handling the tests. The test session was repeated in the other DBS state using the same EC/EO order. Tests started 30 minutes after programming the DBS (i.e. OFF or ON). The full effects of withdrawal of both the DBS and anti-PD medications, and before DBS is at full effect, may vary across a PD population. Hence, a counter-balanced test order design was used to minimize any systematic effects from ON/OFF changes on the recordings. In controls, test order (EC/EO) was randomized using a Latin square.

Experimental design

Participants stood upright on a force platform, with their eyes either closed (EC) or open (EO), in a task that involved an initial period of quiet stance followed by balance perturbations through calf muscle vibration, see figure 1. A force platform (custom-built by the Department of Automatic Control, Lund University, Sweden) recorded ground reaction torques with six degrees of freedom (d.f.) using force transducers with an accuracy of 0.5N. A software program (Postcon™, custom-built by the Department of Clinical Sciences, Lund University, Sweden) controlled the vibratory stimulation and sampled the force platform data at 50Hz using a 16-bit AD-board (PCI-6036E, National Instruments). The participants were exposed to

randomized balance perturbations induced by vibrators strapped over the gastrocnemii (calf) muscles. The vibrators (6cm long and 1cm in diameter) produced a vibration amplitude of 1.0mm and frequency of 85Hz. Both balance tests with eyes closed and eyes open were 235 seconds long. Before a 200-second vibration sequence commenced, a 35-second period of quiet stance was recorded to ensure that no spectral activity was being produced by the vibratory stimulation. The vibratory stimulations were applied as a sequence of multiple balance perturbations produced by turning on and off the vibrators, and where both the vibration ON and OFF state durations ranged from 0.8 to 6.4 seconds, according to a pseudorandom binary sequence (PRBS) schedule [35]. An identical stimulation sequence was used for all participants and in all tests. We analyzed stability during the quiet stance period (0-35s) and during vibratory stimulation as five 35-second time periods; Period 1 from 35-70s; Period 2 from 70-105s; Period 3 from 105-140s; Period 4 from 140-175s and Period 5 from 175-210s. During all five stimulation sequence periods analyzed, the PRBS schedule yielded a similar effective bandwidth of the vibration stimulus in the region of 0.1-2.5Hz, as validated by fast Fourier transformation (FFT) analyses.

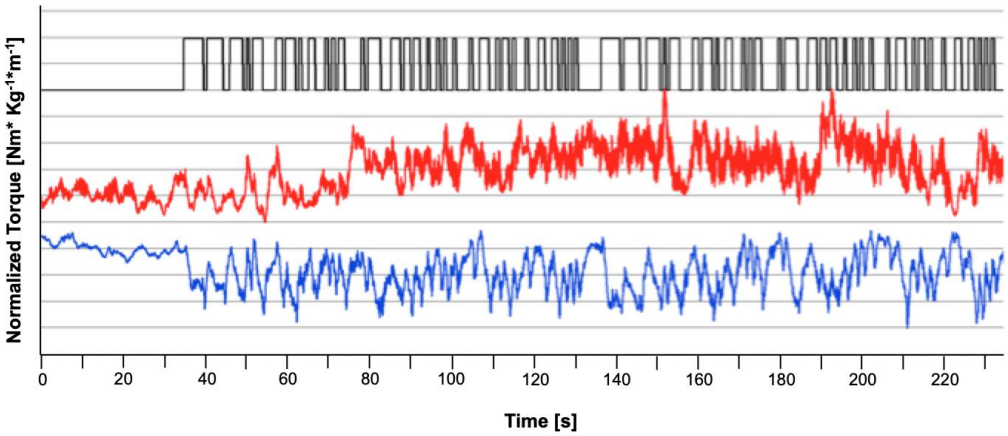

Figure 1. Force platform recording of anteroposterior torque from one PD subject standing with eyes open with the DBS turned OFF (red line) and when the same PD subject perform the test with DBS ON (blue line). When the vibration is turned on and off is marked with a black line. A tremor is clearly visible in the force platform recordings when the DBS is turned OFF, which seemingly is accentuated during quiet stance and during the second half of the posturography test.

With the vibrators attached, each participant was instructed to stand in an erect and relaxed posture, barefoot on the force platform, with arms folded across the chest. The participant's heels were 3cm apart and feet at an angle of approximately 30º open to the front using guidelines. Participants stood 1.5m away from a wall and instructed to focus on a 4 x 6cm image directly ahead at eye level or stand with their eyes closed. All participants were naive to the stimulus and were not informed about the effect calf vibration would have on their balance. They listened to calm classical music through headphones during tests to reduce movement references from external noise sources and to avoid extraneous sound distractions. A five-minute rest period was given to participants between EO and EC tests. Participants with PD were given at least a 30-minute break between ON/OFF changes of DBS.

Power analyses were done on anteroposterior and lateral torques using an FFT feature in a custom-made program (Postcon™). The average spectral power was

calculated for three frequency bandwidths: 0-4Hz; 4-7Hz and 7-25Hz. These bands were selected as the 4-7Hz band is mainly affected by PD resting tremor [25] and the 7-25Hz band by postural 'action' tremor and harmonic activity [26]. The 0-4Hz lower frequency band corresponds to slower alterations of movement [27-30]. The resulting power spectra within each bandwidth represent a measure of energy used towards the surface within these frequency ranges by postural control during quiet stance and balance perturbations. Before the FFT analysis, data from the force platform were normalized to account for anthropometrical differences between participants. Hence, the force platform FFT analysis was performed on raw data normalized with the subject's weight and height, with the normalized unit and scale being [(N m Kg^{-1} m^{-1})·100]. The measurement data were converted into 300 FFT samples reflecting the spectral power in the frequency range from 0.08-25Hz. The spectral power was calculated through a Hamming signal filter window and an averaging procedure using Root Mean Square (RMS). To enhance the robustness of the analysis, the final spectral power spectrum was calculated as average values from 10 repeated spectral power analyses on raw data shifted one sample before each repeated FFT calculation. The average power spectrum for the 10 repeated FFT calculations was calculated using linear weighting.

Statistical Analysis

Log-transformed, mean spectral power values, in anteroposterior and lateral directions and in three spectral bandwidths (0-4Hz; 4-7Hz and 7-25Hz), were analyzed with repeated measures General Linear Model (GLM) Analysis of Variance (ANOVA). The repeated measures GLM ANOVA method was used after ensuring that all dataset combinations analyzed in the study with this statistical

method produced model residuals that had normal or close to normal distribution, thus validating its appropriateness (i.e., whether the GLM ANOVA method was appropriate for correctly analyzing the data) [36]. The main factor combinations analyzed for their effects on stability during balance perturbations from calf vibration were:

1) Group (Controls vs PD with DBS OFF, df 1), Vision (Eyes Open vs. Eyes Closed, df 1) and Repetition (Vibration periods 1-5, df 4); where the model parameter Group is a Between-Subjects factor and where the model parameters Vision and Repetition are Within-Subjects variables.

2) Group (Controls vs PD with DBS ON, df 1), Vision (Eyes Open vs. Eyes Closed, df 1) and Repetition (Vibration periods 1-5, df 4); where the model parameter Group is a Between-Subjects factor and where the model parameters Vision and Repetition are Within-Subjects variables.

3) DBS (PD with DBS ON vs PD with DBS OFF, df 1), Vision (Eyes Open vs. Eyes Closed, df 1) and Repetition (Vibration periods 1-5, df 4); where the model parameter DBS, Vision and Repetition are Within-Subjects variables.

The main factor combinations analyzed for their effects on the stability during quiet stance were:

1) Group (Controls vs PD with DBS OFF, df 1) and Vision (Eyes Open vs. Eyes Closed, df 1); where the model parameter Group is a Between-Subjects factor and where the model parameter Vision is a Within-Subjects variable.

2) Group (Controls vs PD with DBS ON, df 1) and Vision (Eyes Open vs. Eyes Closed, df 1); where the model parameter Group is a Between-Subjects factor and where the model parameter Vision is a Within-Subjects variable.

3) DBS (PD with DBS ON vs PD with DBS OFF, df 1) and Vision (Eyes Open vs. Eyes Closed, df 1); where the model parameters DBS and Vision are Within-Subjects variables.

For post-hoc analysis, we carried out within-subjects paired comparisons to study the effects of DBS and Vision with Wilcoxon matched-pairs signed-rank test (Exact sig. 2-tailed). Between-groups comparisons (controls vs PD with DBS ON and controls vs PD with DBS OFF) were performed with Mann-Whitney U Tests (Exact sig. 2 tailed) [36]. For completeness, a full factorial post hoc analysis was performed on the main factors DBS and Vision, and a partial analysis of Repetition. Adaptation was explored further as the spectral power changes in anteroposterior and lateral directions between vibration period 1 and vibration period 5 as a within-subjects paired comparison using Wilcoxon matched-pairs signed-rank tests (Exact sig. 2-tailed). Bonferroni correction was applied but had no practical effect as all datasets in the statistical within-subjects or between-groups evaluations were included only once in a comparison. Non-parametric statistics were used in the statistical evaluation as not all data sets were normally distributed before or after logarithmic transformation. In the statistical analyses, p-values <0.05 were considered significant.

Results

Spectral analysis of anteroposterior stability during balance perturbations

For anteroposterior power, repeated measures GLM ANOVA of the model (Group, Vision, Repetition) (Table 2) showed that the main factor Group produced no significant influence on power within any frequency range and Group constellation. The significant results for the main factor Vision revealed that lower

levels of power were used with eyes open compared to eyes closed in all bandwidths and across group constellations ($p<0.001$). Analysis of the main factor Repetition revealed that calf vibration produced a significant reduction of power across the vibration periods ($p\leq0.003$) in all bandwidths and group constellations.

The main factor interaction Group x Vision analysis showed a weaker contribution of vision in reducing power in PD with DBS OFF compared to controls in the 7-25Hz band ($p=0.034$). The main factor interaction Group x Repetition analysis showed that controls had better adaptation during calf vibration than participants with PD with DBS OFF in the 4-7Hz band ($p=0.016$) and with DBS ON in all bandwidths ($p\leq0.043$).

Table 2. Repeated measures GLM ANOVA of Group, Vision and Repetition on anteroposterior spectral power during balance perturbations

Anteroposterior spectral power *	Group	Vision	Repetition	Group x Vision	Group x Repetition	Vision x Repetition	Group x Vision x Repetition
Control vs. DBS OFF							
0 - 4 Hz	0.623 [0.2]	**< 0.001 [39.8]**	**< 0.001 [107.5]**	0.262 [1.3]	0.145 [2.3]	0.422 [0.7]	0.540 [0.4]
4 - 7 Hz	0.502 [0.5]	**< 0.001 [22.9]**	**0.003 [11.0]**	0.082 [3.3]	**0.016 [6.9]**	0.148 [2.3]	0.495 [0.5]
7 - 25 Hz	0.629 [0.2]	**< 0.001 [30.4]**	**0.012 [7.5]**	**0.034 [5.2]**	0.090 [3.2]	0.136 [2.4]	0.500 [0.5]
Control vs. DBS ON							
0 - 4 Hz	0.742 [0.1]	**< 0.001 [71.7]**	**< 0.001 [49.4]**	0.942 [0.0]	**0.003 [10.7]**	0.160 [2.1]	0.074 [3.5]
4 - 7 Hz	0.989 [0.0]	**< 0.001 [44.0]**	**< 0.001 [15.8]**	0.395 [0.8]	**0.009 [8.1]**	0.334 [1.0]	0.178 [1.9]
7 - 25 Hz	0.765 [0.1]	**< 0.001 [51.6]**	**0.002 [11.9]**	0.582 [0.3]	**0.043 [4.6]**	0.293 [1.2]	0.074 [3.5]

* Repeated measures GLM ANOVA of anteroposterior spectral power with main factors "Group", "Vision" and "Repetition" and their factor interactions. The notation "<0.001" means that the p-value is smaller than 0.001. F-values are presented in the squared parenthesis.

The repeated measures GLM ANOVA of the model (DBS, Vision, Repetition) (Table 3) showed that the main factor DBS produced no significant influence on power within any frequency range. The significant results for the main factor Vision revealed that lower levels of power were used with eyes open compared to eyes closed in all bandwidths ($p \leq 0.015$). Analysis of the main factor Repetition revealed that calf vibration produced a significant reduction of power across the vibration periods ($p \leq 0.047$) demonstrating adaptation in all bandwidths, apart from the 4-7Hz band for participants with PD OFF.

The main factor interaction DBS x Repetition showed that the adaptation was better in PD with DBS ON than DBS OFF in the 4-7Hz band ($p=0.047$). The main factor interaction DBS x Vision x Repetition showed that adaptation was better in participants with PD with DBS ON than DBS OFF with eyes open in the 7-25Hz band ($p=0.029$).

Table 3. Repeated measures GLM ANOVA of DBS, Vision and Repetition on anteroposterior spectral power during balance perturbations

Anteroposterior spectral power **	DBS	Vision	Repetition	DBS x Vision	DBS x Repetition	Vision x Repetition	DBS x Vision x Repetition
DBS OFF vs DBS ON							
0 - 4 Hz	0.292 [1.3]	**0.004** **[21.0]**	**< 0.001** **[79.3]**	0.090 [4.1]	0.111 [3.5]	0.226 [1.8]	0.380 [0.9]
4 - 7 Hz	0.146 [2.8]	**0.009** **[14.2]**	0.059 [5.4]	0.171 [2.4]	**0.047** **[6.2]**	0.668 [0.2]	0.156 [2.6]
7 - 25 Hz	0.320 [1.2]	**0.015** **[11.3]**	**0.047** **[6.2]**	0.184 [2.3]	0.329 [1.1]	0.141 [2.9]	**0.029** **[8.2]**

** Repeated measures GLM ANOVA of anteroposterior spectral power with main factors "DBS", "Vision" and "Repetition" and their factor interactions.

Post hoc analysis of DBS

In participants with PD, power was significantly higher with DBS OFF compared to DBS ON during four vibration periods in the 4-7Hz band with eyes open ($p \leq 0.014$) (Figure 2). Power in the 7-25Hz band with eyes open was significantly higher in DBS OFF compared to DBS ON during two periods ($p \leq 0.037$).

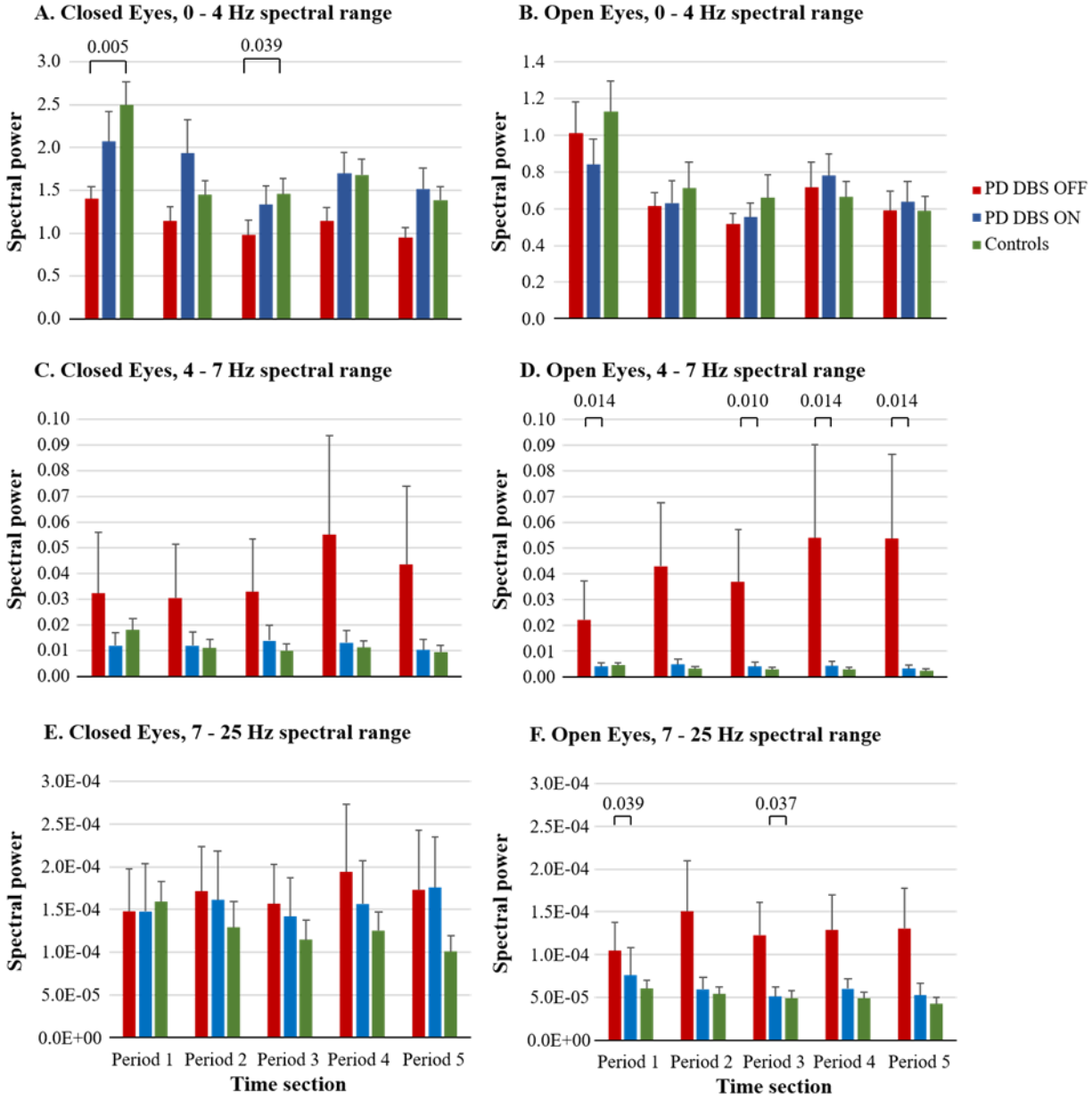

Figure 2. Spectral power of anteroposterior power during the five vibration periods; A) Closed eyes 0-4 Hz band, B) Open Eyes 0-4 Hz band, C) Closed eyes 4-7 Hz spectra, D) Open Eyes 4-7 Hz band, E) Closed eyes 7-25 Hz band, F) Open Eyes 7-25 Hz band.

Post hoc analysis of Vision

During calf vibration, power was lower with eyes open compared to closed in all bandwidths and during all periods in controls ($p<0.001$) and with DBS ON ($p\leq0.020$) (Table 4A). With DBS OFF, power was lower with eyes open compared to eyes closed in only two of the five periods in each bandwidth ($p\leq0.020$).

Table 4. Paired statistical results on (A) anteroposterior and (B) lateral spectral power between Eyes Closed and Eyes Open tests

A. Anteroposterior spectral power	Quiet stance	Period 1	Period 2	Period 3	Period 4	Period 5
Control						
0 - 4 Hz	0.089	**< 0.001**	**0.001**	**< 0.001**	**< 0.001**	**< 0.001**
4 - 7 Hz	0.057	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
7 - 25 Hz	0.132	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
DBS ON						
0 - 4 Hz	0.105	**0.010**	**0.002**	**0.002**	**0.004**	**0.004**
4 - 7 Hz	**0.004**	**0.002**	**0.020**	**0.006**	**0.010**	**0.004**
7 - 25 Hz	0.131	**0.014**	**0.010**	**0.006**	**0.006**	**0.010**
DBS OFF						
0 - 4 Hz	0.203	0.301	**0.020**	**0.008**	0.156	0.109
4 - 7 Hz	0.250	**0.004**	0.910	0.074	**0.016**	0.156
7 - 25 Hz	**0.020**	**0.004**	0.098	0.203	0.156	**0.016**

B. Lateral spectral power	Quiet stance	Period 1	Period 2	Period 3	Period 4	Period 5
Control						
0 - 4 Hz	0.954	**0.002**	**0.011**	0.174	**0.002**	**0.007**
4 - 7 Hz	0.051	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
7 - 25 Hz	0.292	**< 0.001**	**0.003**	**< 0.001**	**< 0.001**	**< 0.001**
DBS ON						
0 - 4 Hz	0.322	0.193	0.064	**0.037**	0.064	**0.002**
4 - 7 Hz	0.084	**0.006**	**0.004**	**0.006**	**0.004**	**0.002**
7 - 25 Hz	0.172	**0.012**	**0.037**	**0.020**	**0.027**	**0.004**
DBS OFF						
0 - 4 Hz	0.074	0.570	**0.004**	**0.004**	**0.016**	**0.047**
4 - 7 Hz	0.496	**0.020**	0.164	0.074	**0.031**	0.078
7 - 25 Hz	0.129	**0.039**	0.098	0.359	**0.031**	0.078

Post hoc analysis of adaptation to balance perturbation in PD

In controls, post hoc statistics showed that calf vibration caused a cumulative adaptation of about 42% on average with eyes closed in all bandwidths ($p<0.001$) and about 40% on average with eyes open in all bandwidths ($p\leq0.015$) (Table 5). However, in participants with PD, significant adaptation was only found in the 0-4Hz bandwidth with eyes closed with DBS ON ($p=0.049$, 27% energy reduction). With DBS OFF, there was significant adaptation with eyes open in the 0-4Hz band ($p=0.014$, 41% reduction) but with eyes closed power increased in the 0-4Hz band ($p=0.016$, 34% energy increase).

Table 5. Spectral power changes in anteroposterior and lateral directions between vibration period 1 and vibration period 5.

Stability changes [+]		Anteroposterior		Lateral	
		Vibration Period 1 vs Period 5		Vibration Period 1 vs Period 5	
		Eyes Closed	Eyes Open	Eyes Closed	Eyes Open
Controls					
	0 - 4 Hz	**< 0.001 (0.56)**	**< 0.001 (0.52)**	**< 0.001 (0.48)**	**< 0.001 (0.46)**
	4 - 7 Hz	**< 0.001 (0.53)**	**0.002 (0.57)**	**< 0.001 (0.24)**	**0.001 (0.38)**
	7 - 25 Hz	**< 0.001 (0.64)**	**0.015 (0.70)**	**< 0.001 (0.72)**	**0.017 (0.79)**
DBS ON					
	0 - 4 Hz	**0.049 (0.73)**	0.193 (0.75)	0.846 (0.99)	0.105 (0.50)
	4 - 7 Hz	0.557 (0.85)	0.064 (0.82)	0.922 (1.17)	0.105 (0.80)
	7 - 25 Hz	0.846 (1.19)	0.232 (0.70)	0.266 (0.89)	0.846 (0.92)
DBS OFF					
	0 - 4 Hz	**0.016 (1.34)**	**0.014 (0.59)**	0.578 (0.75)	**0.027 (0.43)**
	4 - 7 Hz	0.844 (1.17)	0.770 (2.41)	0.078 (0.95)	0.922 (3.66)
	7 - 25 Hz	0.578 (0.59)	0.625 (1.25)	0.109 (0.83)	0.375 (1.20)

[+] The quotient value between period 1 and period 5 is presented within the parenthesis. A quotient value above signifies a worsening performance over time, i.e., that the spectral power was higher in Period 5 compared to Period 1.

Spectral analysis of lateral stability during balance perturbations

For lateral power, repeated measures GLM ANOVA of the model (Group, Vision, Repetition) (Table 6) showed that the main factor Group produced no significant influence on power within any frequency range and Group constellations. The significant results for the main factor Vision revealed that lower levels of power were used with eyes open compared to eyes closed in all group constellations and in all bandwidths ($p<0.001$). Analysis of the main factor Repetition revealed that calf vibration produced a significant reduction of power across the vibration periods in all group constellations demonstrating adaptation, and in all bandwidths ($p\leq0.007$).

The main factor interaction Group x Repetition showed that controls had better adaptation compared to participants with PD with DBS ON in the 0-4 Hz band ($p=0.016$). The main factor interaction Vision x Repetition showed poorer adaptation with eyes open compared to eyes closed in the 7-25Hz band for DBS OFF compared to controls ($p=0.044$) and poorer adaptation with eyes open for DBS ON compared to controls in the 4-7Hz band ($p=0.049$). The interaction Group x Vision x Repetition revealed that adaptation was better in controls compared to participants with PD with DBS OFF ($p=0.044$) and DBS ON in the 4-7Hz band with eyes open ($p=0.029$).

Table 6. Repeated measures GLM ANOVA of Group, Vision and Repetition on lateral spectral power during balance perturbations

Lateral spectral power*	Group	Vision	Repetition	Group x Vision	Group x Repetition	Vision x Repetition	Group x Vision x Repetition
Control vs. DBS OFF							
0 - 4 Hz	0.061 [3.9]	**< 0.001 [40.4]**	**< 0.001 [40.4]**	0.233 [1.5]	0.307 [1.1]	0.214 [1.6]	0.378 [0.8]
4 - 7 Hz	0.056 [4.1]	**< 0.001 [49.6]**	**0.003 [21.8]**	0.079 [3.4]	0.099 [3.0]	0.095 [3.1]	**0.038 [4.9]**
7 - 25 Hz	0.120 [2.6]	**< 0.001 [28.1]**	**0.004 [10.3]**	0.318 [1.0]	0.067 [3.7]	**0.044 [4.6]**	0.162 [2.1]
Control vs. DBS ON							
0 - 4 Hz	0.068 [3.7]	**< 0.001 [28.5]**	**< 0.001 [17.4]**	0.942 [0.0]	**0.016 [6.7]**	0.228 [1.5]	0.062 [3.8]
4 - 7 Hz	0.236 [1.5]	**< 0.001 [82.7]**	**< 0.001 [60.8]**	0.416 [0.7]	0.099 [2.9]	**0.049 [4.3]**	**0.029 [5.4]**
7 - 25 Hz	0.232 [1.5]	**< 0.001 [36.1]**	**0.007 [8.6]**	0.675 [0.2]	0.064 [3.8]	0.204 [1.7]	0.113 [2.7]

* Repeated measures GLM ANOVA of lateral spectral power with main factors “Group”, “Vision” and “Repetition” and their factor interactions.

The repeated measures GLM ANOVA of the model (DBS, Vision, Repetition) (Table 7) showed that the main factor DBS produced no significant influence on the stability within any frequency range. The significant results for the main factor Vision revealed that lower levels of power were used with eyes open compared to eyes closed in all bandwidths ($p \leq 0.024$). Analysis of the main factor Repetition revealed that calf vibration produced a significant reduction of power across the vibration periods in all bandwidths ($p \leq 0.013$) apart from the 7-25Hz band.

The main factor interaction DBS x Vision x Repetition revealed that adaptation was better in PD with DBS ON compared to DBS OFF with eyes open ($p=0.026$).

Table 7. Repeated measures GLM ANOVA of DBS, Vision and Repetition on lateral spectral power during balance perturbations

Lateral spectral power **	DBS	Vision	Repetition	DBS x Vision	DBS x Repetition	Vision x Repetition	DBS x Vision x Repetition
DBS OFF vs DBS ON							
0 - 4 Hz	0.525 [0.5]	**0.014 [11.7]**	**0.004 [20.9]**	0.096 [3.9]	0.298 [1.3]	0.324 [1.2]	0.579 [0.3]
4 - 7 Hz	0.084 [4.3]	**0.005 [19.2]**	**0.013 [12.0]**	0.233 [1.8]	0.131 [3.0]	0.715 [0.1]	**0.026 [8.6]**
7 - 25 Hz	0.132 [3.0]	**0.024 [8.9]**	0.080 [4.4]	0.437 [0.7]	0.241 [1.7]	0.331 [1.1]	0.143 [2.8]

** Repeated measures GLM ANOVA of lateral spectral power with main factors “DBS”, “Vision” and “Repetition” and their factor interactions.

Post hoc analysis of DBS

In PD, power was higher for DBS OFF compared to DBS ON in the 4-7Hz band in two vibration periods with eyes closed ($p \leq 0.027$) and in four periods with eyes open ($p \leq 0.014$) (Figure 3). The power in the 7-25Hz band was significantly higher for DBS OFF compared to DBS ON in one period with eyes closed ($p=0.016$) and in four periods with eyes open ($p \leq 0.049$).

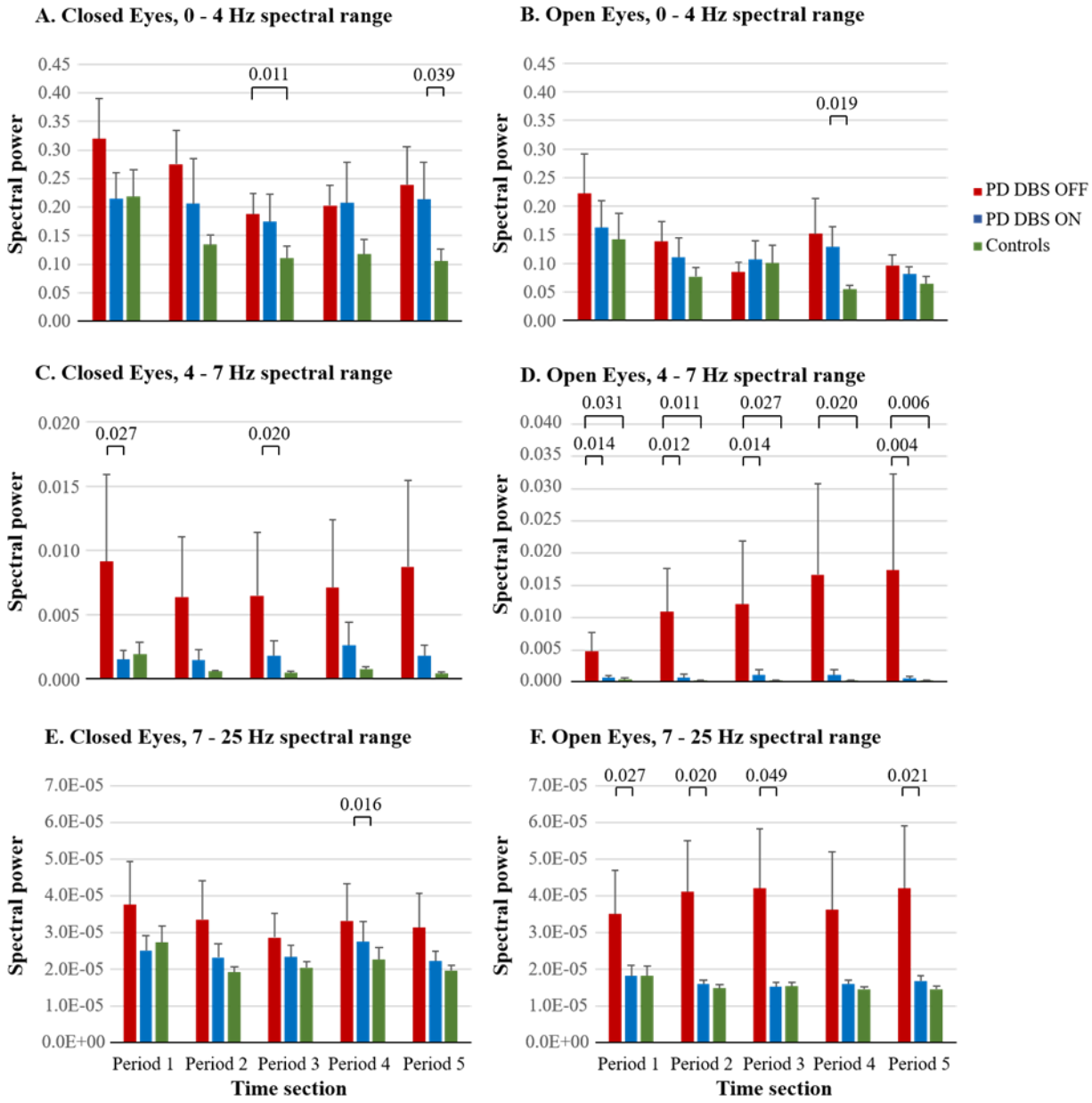

Figure 3. Spectral power of lateral power during the five vibration periods; A) Closed eyes 0-4 Hz band, B) Open Eyes 0-4 Hz band, C) Closed eyes 4-7 Hz band, D) Open Eyes 4-7 Hz band, E) Closed eyes 7-25 Hz band, F) Open Eyes 7-25 Hz band.

Post hoc analysis of Vision

In controls, power was lower with eyes open compared to eyes closed in all bandwidths and periods ($p \leq 0.011$) except in the 0-4Hz band in one period (Table 4B).

There was a significant reduction of power with eyes open compared to eyes closed in PD with DBS ON in all bandwidths and periods ($p \leq 0.037$) except in the 0-4Hz band in three periods. However, in PD with DBS OFF there was a significant reduction of power with eyes open compared to eyes closed in four vibration periods in the 0-4Hz band and in two vibration periods in the 4-7Hz and 7-25Hz bands ($p \leq 0.047$).

Post hoc analysis of adaptation to balance perturbation in PD

In controls, post hoc statistics revealed that calf vibration caused a cumulative adaptation of about 52% on average with eyes closed in all bandwidths ($p < 0.001$) and about 46% on average with eyes open in all bandwidths ($p \leq 0.015$) (Table 5). However, no significant adaptation was found for DBS ON in any bandwidth or period. In PD with DBS OFF, significant adaptation was only found in the 0-4Hz bandwidth with eyes open ($p = 0.027$, 57% energy decrease).

Spectral analysis of quiet stance

For quiet stance, GLM ANOVA showed no significant difference for Group or Vision between PD participants with their DBS ON vs OFF or compared to Controls in the anteroposterior and lateral directions. For completeness, the pairwise statistics for quiet stance are shown in Figure 4.

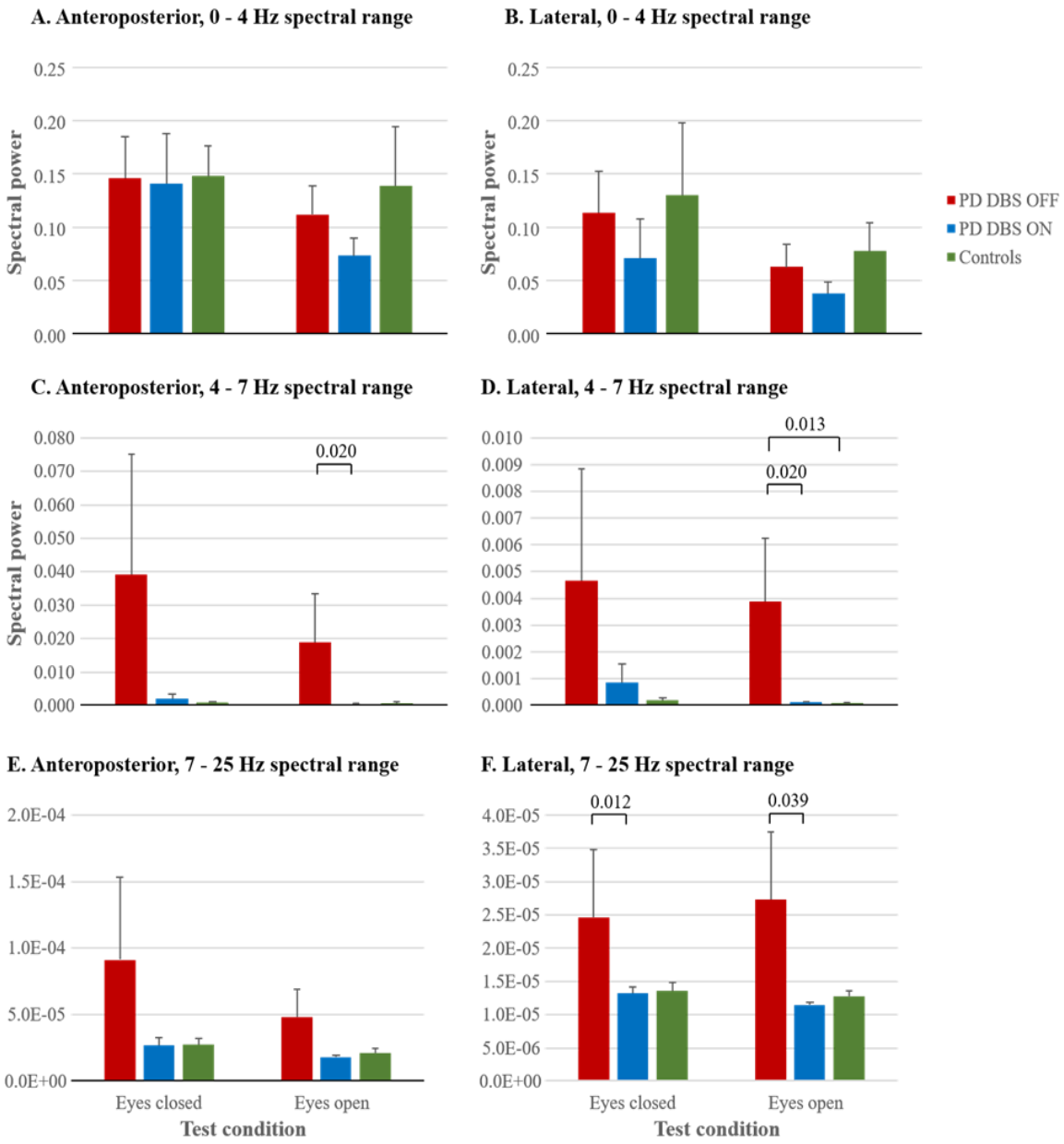

Figure 4. Spectral power during quiet stance; A) Anteroposterior direction 0-4 Hz band, B) Lateral direction 0-4 Hz band, C) Anteroposterior 4-7 Hz band, D) Lateral 4-7 Hz band, E) Anteroposterior 7-25 Hz band, F) Lateral 7-25 Hz band.

Summary analysis of DBS

To summarize, DBS significantly reduced anteroposterior and lateral energy used in 4-7Hz and 7-25Hz frequency bands but not 0-4Hz. These effects were

present in the vibration periods in a lateral direction with eyes open and eyes closed and in anteroposterior direction with eyes open (Table 8).

Table 8. Paired statistical results between DBS OFF and DBS ON in Quiet Stance (QS) and vibration periods 1-5 in anteroposterior (A) and lateral (B) directions with Eyes Closed and Eyes Open.

A. Anteroposterior spectral power		QS	P1	P2	P3	P4	P5
Eyes Closed							
	0-4Hz	0.910	0.250	0.359	0.652	0.219	0.297
	4-10 Hz	0.250	0.250	0.164	0.301	0.078	0.219
	10-25 Hz	0.129	0.301	1.000	0.734	0.297	0.156
Eyes Open							
	0-4Hz	0.250	0.652	0.770	0.922	0.492	0.922
	4-7 Hz	**0.020**	**0.014**	0.084	**0.010**	**0.014**	**0.014**
	7-25 Hz	0.129	**0.039**	0.105	**0.037**	0.084	0.064

B. Lateral spectral power		QS	P1	P2	P3	P4	P5
Eyes Closed							
	0-4Hz	0.129	0.359	0.359	0.820	0.156	0.297
	4-10 Hz	0.164	**0.027**	0.129	**0.020**	0.078	0.078
	10-25 Hz	**0.012**	0.098	0.121	0.098	**0.016**	0.172
Eyes Open							
	0-4Hz	0.275	0.375	0.770	0.695	0.770	0.695
	4-7 Hz	**0.020**	**0.014**	**0.012**	**0.014**	0.084	**0.004**
	7-25 Hz	**0.039**	**0.027**	**0.020**	**0.049**	0.084	**0.021**

Discussion

In this study, we conducted a wide spectral analysis of torque during quiet stance and repeated balance perturbations in participants with PD and isolated effects into bands to quantify the dynamics and determine the effects of using the technology of bilateral DBS STN and visual feedback. We did this because the standard approach to tremor and stability control evaluation in medical practice is subjective scoring, e.g., that an evaluator observes the body movements and then rates the performance

with a number (from 0 to 4 in the UPDRS). Our results confirmed our hypothesis that DBS STN reduces higher frequency spectral power (4-25Hz) but not lower frequency spectral power (≤4Hz) (Figure 1).

Effect of DBS STN

Our previous work showed no significant difference between DBS ON and DBS OFF for torque variance during balance perturbations in participants with PD [32], a finding echoed by other groups [4-6]. In the current study, 0–4Hz spectral power was not significantly reduced by DBS during balance perturbations, but spectral power >4Hz was (Table 6). This applied to both anteroposterior and lateral spectral power. The beneficial effects of DBS ON were also shown by reductions of spectral power with eyes open compared with eyes closed.

The finding that DBS STN did not significantly decrease spectral power ≤4Hz is corroborated by previous work showing that postural sway between 3-4Hz is unrelated to tremor amplitude in participants with PD, but postural sway >4Hz is related to tremor amplitude [37]. In other words, DBS STN appears to exert its effects on postural control through the suppression of tremor >4Hz as it is well known that the 4-7Hz band is mainly affected by PD resting tremor [25]. Further is the reduction of power spectra in the 7-25Hz bandwidth which corresponds to postural 'action' tremor and harmonic activity [26]. The most plausible explanation is that the suppression of PD resting tremor eliminated the underlying harmonic activity in the 7-25Hz band. However, growing evidence suggests that DBS acts "through multimodal mechanisms that are not limited to inhibition and excitation of basal ganglia circuits" [38] and its therapeutic effects may extend over a range of functions. One possibility is that DBS STN has an effect on power spectra between

7-25Hz through frontal lobe activation of non-dopaminergic pathways [39] but making further comment goes beyond the scope of the current study.

Effects of DBS on Vision

The important contribution of vision for postural control in healthy individuals is well known [40], where postural sway is smaller with eyes open compared to eyes closed, particularly when balance is perturbed [41, 42]. However, we found a general reduction to the contribution of vision in participants with PD with DBS OFF across all frequency ranges during vibration (Table 3). Power was not significantly smaller with eyes open compared to eyes closed across all spectral ranges. In normal conditions, vision provides a frame of reference, where a postural imbalance can be quickly detected and an appropriate response can be initiated to maintain postural stability [43, 44]. However, in PD with DBS OFF, an alteration to the visual contribution to postural control would place greater reliance on other sensory sources [20]. An implication of this is for patients who require their DBS to be switched OFF temporarily or stimulation parameters adjusted as the sensory contributions to postural control are altered which may lead to initial postural imbalance.

The visual contribution to posture is usually investigated by studying visually induced postural reactions to moving scenes [45]. Such studies have shown that participants with PD express larger postural responses compared to controls or patients with cerebellar syndromes [20]. However, in the current study, we have quantified the contribution of vision between eyes open and eyes closed tests and between groups across spectral frequencies to consider the postural dynamics. This method has shown a different effect, that for upright postural control with DBS

OFF, visual information does not contribute highly to maintaining stability. The two results, that participants with PD express heightened postural responses to moving scenes and that there is a reduced contribution of vision during external balance perturbations to the frequency power spectra, are not incongruent. Both results point to a central processing deficit in relation to the integration of visual cues. Further support for a central processing deficit in the current study is that visual information contributed more to postural stability in PD with DBS ON. A sensory processing deficit has also been identified in patients with PD by Hwang and colleagues [45] using different modes of sensory stimulation – moving scenes, proprioceptive vibration and galvanic vestibular stimulation - to determine the level of sensory re-weighting. In their study, Hwang and colleagues found a similar end-result to ours, where there was no reweighting of visual information in PD when proprioception was altered through Achilles tendon vibration.

Effect of DBS on Adaptation

Our ability to adapt based on prior experience is important for fall prevention [44, 46] and negotiating changing environments [47, 48]. One of the main roles of the basal ganglia is the appropriate selection of motor or behavioral programs for a given environment and therefore the basal ganglia has a crucial role in motor learning [49]. However, studies suggest that the acquisition as well as retention of motor learning in PD is preserved albeit with a slower rate of motor learning [50]. Consistent with the latter, we found that anteroposterior and lateral postural adaptation were impaired with eyes open and eyes closed and with both DBS ON and OFF in PD compared to controls. Control participants were able to adapt to the balance perturbations from calf vibration but participants with PD almost always

failed to do so, especially in the spectral power range >4Hz (Table 4). Some participants with with PD even increased their spectral power between vibration periods 1 and 5 showing difficulty in adapting to novel situations, a finding that has been shown previously by Bronstein and colleagues (1990) [20]. Our findings also corroborate the results of Hall and colleagues (2013) [51], who demonstrated that PD diminishes the ability to refine postural strategies ON levodopa therapy, but in contrast to our results, they found no impairment of adaptation in an OFF levodopa state. This perhaps implies a reduced level of motor adaptation related to dopamine changes. Another feature is that the individuals with PD in the current study required DBS and but in participants with PD without DBS adaptation appears to be preserved [52].

It is well known that patients with PD experience postural instability to short-lasting, phasic perturbations that occur over seconds [53], but studies that perturb balance over minutes are limited. One leading view is that because anticholinergic medication, which modulates the activity between the pedunculopontine nucleus (PPN) laterodorsal tegmental complex and brainstem structures, exacerbates postural instability and falls [54], the loss of PPN cells in PD is one of the main causes of postural instability in PD [55]. Further support for this view comes from clinical studies showing that the acetylcholinesterase inhibitor, donepezil, is associated with a reduced risk of falls in PD [56]. The involvement of these brain structures in postural stability has led researchers to use DBS of the PPN as a potential therapy [57] but this has produced inconsistent results [58]. The loss of PPN cells therefore offers another possible explanation for the reduced adaptation across spectral frequencies.

A global analysis of brain regions associated with motor learning revealed a bilateral cortical-subcortical network including the putamen alongside the dorsal premotor cortex, supplementary motor cortex, primary motor cortex, primary somatosensory cortex, superior parietal lobule, thalamus and cerebellum [51]. Notably, the putamen is directly responsible for the selection of the movement strategy and the automatic performance of previously learned movements [59]. However, it is likely that alterations in various brain areas that include cortical and subcortical structures accounts for the loss of postural adaptation in the spectral power that we observed. Postural adaptation depends on the production of accurate counter-responses and background muscle tone to counter the effects of gravity and coordinate the various body sections. As both the rapid counter-measures and to a lesser degree the maintenance of muscle tone are affected when perturbations are repeated in participants with PD, with DBS ON and DBS OFF, we show that there remains a fall risk following DBS. Although slow alterations of posture are mediated by tonic muscle contractions generated by sub-cortical nuclei, the postural counter-measures may be generated either reflexively or voluntarily. As such, various brain regions are likely to be involved and neuroimaging would be required to isolate those responsible for the reduced levels of adaptation in participants with PD in this task.

Study limitations

This study has some methodological limitations, which includes the small sample size and that our tests are conducted during stance although most falls occur while walking. It also needs noting that we challenged postural stability using external perturbations whereas in daily life balance is generally perturbed by self-

generated perturbations. However, others have also noted significant effects using a similar number of participants and protocol [17].

Another limitation is that the control group was about 7 years older on average to the PD group. We do not expect this difference in mean age to affect our results. Moreover, if there was an age effect, this would increase power in the control group and work against our hypothesis. Our results showed that controls expressed lower power to participants with PD. However, DBS generally reduced power in participants with PD and the difference between groups.

Conclusion

Our study shows that the current way of assessing tremor and stability in clinical practice can be markedly improved by applying objective and sensitive computational methods that quantify spectral changes from postural recordings. Here, signal processing of postural control data proved to be one such method of analysis that for participants with PD provided sensitive, quantitative and objective information about tremor and stability characteristics. Using such methods, we were able to reveal that the DBS STN technology altered the spectral characteristics of postural control in participants with PD through a reduction of power used >4Hz. Moreover, the DBS STN tended to increase the stabilizing effect of vision in all spectral frequencies. However, the DBS STN technology did not restore the adaptive abilities in motor control mechanisms in our patients. The control group was able to adapt their postural control within all spectral bandwidths. The PD patients on the other hand, adapted their postural control in the low spectral band (<4 Hz) with the DBS device ON but an adaptation was absent in all spectral frequencies with the DBS device turned OFF. Furthermore, this study highlights the

importance of using appropriate sensitive and objective computational assessment methods of the biomedical systems. Clinically, almost all neurology or balance departments use the subjective Unified Parkinson's Disease Rating Scale (UPDRS) as their conventional method of assessing tremor and stability. Some more advanced clinics have force platform hardware available but then commonly only record quiet stance performance for no more than 30s, which means that the opportunity to perform appropriate spectral analysis is very limited. Our results showed that a short quiet stance recording uncovers far less information compared with longer recordings that include challenging balance perturbations. Balance perturbations are used in more advanced posturography tests as the increased postural challenge enhances the ability to reveal pathologies and the contribution from vision for postural control [13, 14]. In this study, it was also important to ensure that throughout all assessments, the patients should always be in a mode of actively controlling their stability. This study setup enabled us to quantify the properties of the dynamics of PD across a wide bandwidth and characterize changes made in postural dynamics over time. Postural adaptation is not a routine clinical measure in Parkinson's disease diagnosis but our study supports its inclusion. Our computational technique is easy to employ and would help clinicians to identify where and if interventions are having the desired effects and how the dynamics of balance changes.

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Additional information

Competing interests

The authors declare that they have no competing interests.

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