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# **Interactive effects of GPI stimulation and levodopa on postural control in Parkinson's disease**

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## **Abstract**

**Introduction:** Postural instability is a major source of disability in idiopathic Parkinson's disease (IPD). Deep brain stimulation of the globus pallidus internus (GPI-DBS) improves clinician-rated balance control but there have been few quantitative studies of its interactive effects with levodopa (L-DOPA). The purpose of this study was to compare the short-term and interactive effects of GPI-DBS and L-DOPA on objective measures of postural stability in patients with longstanding IPD.

**Methods:** Static and dynamic posturography during a whole-body leaning task were performed in 10 IPD patients with bilateral GPI stimulators under the following conditions: untreated (OFF); L-DOPA alone; DBS alone; DBS+L-DOPA, and in 9 healthy Control subjects. Clinical status was assessed using the UPDRS and AIMS Dyskinesia Scale.

**Results:** Static sway was greater in IPD patients in the OFF state compared to the Control subjects and was further increased by L-DOPA and reduced by GPI-DBS. In the dynamic task, L-DOPA had a greater effect than GPI-DBS on improving Start Time, but reduced the spatial accuracy and directional control of the task. When the two therapies were combined, GPI-DBS prevented the L-DOPA induced increase in static sway and improved the accuracy of the dynamic task.

**Conclusion:** The findings demonstrate GPI-DBS and L-DOPA have differential effects on temporal and spatial aspects of postural control in IPD and that GPI-DBS counteracts some of the adverse effects of L-DOPA. Further studies on larger numbers of patients with GPI stimulators are required to confirm these findings and to clarify the contribution of dyskinesias to impaired dynamic postural control.

## Introduction

Postural instability (PI) is known to be a levodopa-resistant characteristic of advanced idiopathic Parkinson's disease (IPD) that worsens with disease progression [1-3]. High frequency deep brain stimulation of the globus pallidus internus (GPI-DBS) has been shown to elicit significant anti-parkinsonian effects superior to best medical therapy reducing tremor, bradykinesia and rigidity, and suppressing levodopa-induced dyskinesias [4-8].

Historically, studies evaluating the effects of DBS and levodopa (L-DOPA) on postural stability have used clinical rating scales, including the Postural Instability and Gait Disorder (PIGD) component of the Unified Parkinson's Disease Ratings Scale (UPDRS). GPI stimulation in combination with levodopa has been shown to improve PIGD scores [9], as well as alleviating the other cardinal signs of IPD [10]. Most recently, the combined effect of medication and DBS was found to improve subjective balance and gait scores more than either therapy alone [11]. However, the subjective nature of the PIGD and similar rating scales, and its questionable specificity and sensitivity compared to more quantitative measures of PI [3,12] raises questions as to its utility as a measure of postural stability. To date there have been few quantitative studies assessing the effects of DBS, in particular the interactive effects between DBS and levodopa, and these have included only small numbers of GPI-DBS patients [3,13-15].

Quantitative posturography provides a more precise measure of postural stability than the commonly used clinician-rated balance assessments. Using a range of quantifiable measures, such as sway path area and length, a more detailed analysis of changes in postural control with

treatment and disease progression is achievable [16-20]. Moreover, dynamic posturographic measures allow IPD patients who fall to be discriminated from non-fallers [18].

In this study we used static and dynamic posturography to objectively assess the short-term effects on PI of GPI-DBS and L-DOPA, individually and in combination, in a group of patients with advanced IPD with GPI stimulators. An understanding of how the two treatment modalities interact is important as most patients with implanted stimulators still require ongoing treatment with L-DOPA and other dopaminergic medications.

## **Subjects and Methods**

### Subjects

Ten IPD patients (7 males; mean age  $58.8 \pm 5.6$  years; mean disease duration  $13.4 \pm 5.8$  years; mean Hoehn & Yahr score  $2.5 \pm 0.5$ ) from the Movement Disorders Clinic at the Western Australian Neuroscience Research Institute (WANRI) and 9 healthy age-matched Control subjects (6 males; mean age  $60.7 \pm 8.1$  years) gave informed consent to participate in the study, which was approved by the Sir Charles Gairdner Hospital Human Ethics Committee (Approval Number 2006/073). Clinical and demographic features are summarized in Tables 1 and 2. All subjects had bilateral implanted GPI stimulators (mean duration  $29.4 \pm 15.1$  months).

### Experimental Design

Quantitative posturography was used to assess static and dynamic balance under four treatment conditions: 1 - Untreated (OFF); 2 - Levodopa alone (L-DOPA); 3 - DBS alone (DBS); 4 - DBS plus levodopa (DBS+L-DOPA). The sequence of testing involved pairing L-DOPA with DBS

(i.e. L-DOPA with and without DBS; No L-DOPA with and without DBS), and then randomising these pairings on separate days. During Conditions 2 and 4 (i.e. L-DOPA vs DBS+L-DOPA), subjects took their usual dose of levodopa in the fasting state having withheld all anti-parkinsonian medications for 12 hours. Testing commenced during the clinically defined 'ON' state, as determined by their regular treating clinician (JR, who was present), confirmed by concurrence with the patients' subjective knowledge of their typical 'ON' response which occurred within 30-60 minutes in all patients. On both days, the patients were first tested with DBS on, then again 30-60 minutes after switching off the stimulator, confirming the loss of DBS benefit, prior to posturographic assessment by their usual treating clinician (JR). The UPDRS motor assessment was performed immediately prior to posturography in each of the four conditions and after switching off the stimulator, and the AIMS Dyskinesia Scale [21] in conditions 2 and 4. As shown in Table 2, dyskinesias were minor or absent at the time of testing.

### Posturography

Postural measurements were made with patients standing barefoot on a 0.5 x 0.5 m force platform (AccuswayPlus, Advanced Mechanical Technology, Inc.). Foot position was standardized across assessments by constraining the medial heel-to-heel distance to 5 cm, allowing patients to adjust foot rotation to a comfortable angle and subsequently marking these points to define the base of support (BoS) perimeter, defined anteriorly by the tip of the hallux and fifth metatarsal head and posteriorly by the lateral heel borders. The centre of the BoS perimeter (BoS Centre) was used for all subsequent measures.

Centre of pressure (CoP) acquisitions were made during static standing and dynamic balance tasks. During the static standing task, the patient maintained visual fixation on a cross projected

at eye level at a distance of 1 metre while standing as still as possible for 60 seconds with arms by their sides (EO condition). This task was repeated with the eyes closed (EC condition). The task was performed twice for each condition, with a 2-minute seated rest period between tasks.

The dynamic assessment task was designed to assess the ability to move the CoP as rapidly and accurately as possible to a number of eccentric positions with respect to the BoS Centre and to maintain this position for a 1 sec period. Real-time CoP position relative to the BoS perimeter was displayed at a distance of 1 metre from the subject on a 24-inch computer monitor adjusted to eye level. Circular targets were programmed to appear in random order at one of 8 eccentric positions on the screen ( $0^\circ$ ,  $45^\circ$ ,  $90^\circ$ ,  $135^\circ$ ,  $180^\circ$ ,  $225^\circ$ ,  $270^\circ$  and  $315^\circ$  relative to the vertical). Based on previous experience with such studies [18,19], a distance of 35% of the BoS perimeter was chosen to maximise the patient's ability to successfully complete the trial protocol. Patients began the test with the CoP trace in the BoS Centre target marker and were then required to lean as quickly and as accurately as possible so as to move their CoP (indicated by a bright trace) to each of the targets as they appeared. Each target remained illuminated until the subject achieved the required 1 sec targeting period, following which the central target would re-illuminate in preparation for the next movement. Patients controlled movement of their body sway using predominantly an ankle strategy (knees and hips maintained in relaxed neutral alignment), and had a practice trial to ensure full understanding of the activity. They were instructed to hold the CoP trace in each target position for 1 sec before returning to the BoS Central target marker and to then await the appearance of the next target in the programmed sequence.

#### Data and Statistical Analysis

For the static standing task, Sway Path Length (total distance covered by the CoP trace; cm), Sway Area (95<sup>th</sup> percentile of an ellipse fitted to the overall CoP trace; cm<sup>2</sup>) and Movement Speed (cm/sec) were measured as indices of static stance performance. For the dynamic task, the following variables were measured: Start Time (time in seconds to break the boundary of the central target); Target Achievement Time (time in seconds to maintain the predetermined hold time after crossing the perimeter of each eccentric target); Average Speed (cm/sec); Wandering (the CoP path length to make first contact with the designated eccentric target; cm); and Target Overshoot (CoP distance travelled beyond the initial contact with the designated target; cm).

A two-way repeated-measures ANOVA was used to test the measures of static and dynamic posturography across the 4 treatment conditions (OFF vs. L-DOPA vs. DBS vs. DBS-L-DOPA) and 2 eye conditions (Open vs. Closed). A post-hoc Pairwise comparison was used to compare means across the 4 different treatment conditions with a Bonferroni adjustment for multiple comparisons. Independent sample *t*-tests were also used to compare healthy age-matched control subjects to the 4 treatment conditions for static and dynamic posturography measures. Where Mauchly's tests indicated a violation of assumed sphericity, the Greenhouse-Geisser corrected test estimates are reported. All data were analysed using SPSS for Windows version 19 (SPSS Inc, IBM, USA).

## **Results**

The results of the static and dynamic posturography for the IPD patients and Control subjects are summarised in Figure 1 and Table 3.



### Static posturography

Two-way repeated-measures ANOVA showed a significant within-condition effect for both Sway Area ( $F_{(1,9)}=10.34$ ,  $p<0.05$ ) and Sway Path Length ( $F_{(1,9)}=28.41$ ,  $p<0.05$ ). In the OFF state, both Sway Area and Sway Path Length with eyes open were significantly increased compared to Control subjects (by 94.1% and 39.5% respectively,  $p<0.05$ ). In the L-DOPA condition, Sway Area was increased by a further 169.7% compared to the OFF condition and 423.5% compared to Control subjects ( $p<0.05$ ), whereas in the DBS condition, there was a non-significant reduction in Sway Area but not in Sway Path Length. In the DBS+L-DOPA condition, the L-DOPA-induced increase in Sway Area no longer occurred but Sway Area remained significantly increased (88.2%,  $p<0.05$ ) compared to Control subjects. No significant difference in Movement Speed was observed between the four treatment conditions and Control subjects with eyes open and closed.

### Dynamic posturography

Two-way repeated-measures ANOVA showed a significant within-condition effect for Start Time ( $F_{(1,9)}=7.65$ ,  $p<0.05$ ), Achievement Time ( $F_{(1,9)}=5.33$ ,  $p<0.05$ ), Overshoot ( $F_{(1,9)}=6.26$ ,  $p<0.05$ ) and Wandering ( $F_{(1,9)}=10.56$ ,  $p<0.001$ ). Start Time was significantly shorter in the L-DOPA condition compared to the OFF condition (120%,  $p<0.05$ ) and Control subjects (60%,  $p<0.05$ ), but was not affected by DBS alone, whilst DBS+L-DOPA resulted in a less marked reduction than DOPA alone (28.6%,  $p<0.05$ ) (Table 3). In contrast, the Target Achievement Time was longer (82.4%,  $p<0.05$ ) in the L-DOPA condition compared to the OFF condition, but was significantly reduced by DBS+L-DOPA compared to L-DOPA alone ( $p<0.05$ ). Target Overshoot was significantly increased in the L-DOPA condition compared to the OFF condition and Control subjects (680%,  $p<0.05$ ). This

increase was partially reversed in the DBS+L-DOPA condition, though it was still significantly greater compared to the OFF condition and Control subjects. In the L-DOPA condition there was also a marked increase and increased variability in Wandering compared to the OFF condition and Control subjects ( $p < 0.05$ ), which did not occur with DBS+L-DOPA. There were no significant changes in Average Speed for any of the conditions.

### UPDRS Scores

There were significant improvements in the UPDRS motor, tremor and axial scores in both the L-DOPA ( $p < 0.05$ ) and DBS conditions ( $p < 0.05$ ), and there was a trend towards a greater improvement in the DBS+L-DOPA condition, although this was not statistically significant. Regression analysis found no significant correlations existed between UPDRS scores and Sway Area or Sway Path Length, but showed a significant correlation between the AIMS score in the L-DOPA condition and Sway Area ( $p = 0.02$ ), Target Achievement Time ( $p = 0.02$ ), Wandering ( $p = 0.04$ ) and Target Overshoot ( $p = 0.01$ ).

### **Discussion**

This is the largest study of postural control in IPD patients with GPI stimulators using quantitative posturography, and of the interactive effects of GPI-DBS and levodopa. The aim of the study was to better characterise the short-term effects of levodopa and GPI-DBS on objective measures of static and dynamic postural stability, with particular attention to changes between the standard 4-state post-DBS treatment assessment protocol. Novel aspects of the study were the application of a multidirectional dynamic leaning task to assess whole body postural control, and the finding that GPI-DBS improved the spatial accuracy and directional

control of the task when administered during the levodopa ON state. Our findings also confirm previous observations in smaller numbers of patients that GPI-DBS reduces sway during stance and abrogates the increase in sway which occurs on levodopa [3,14].

The findings provide further evidence for the differential effects and mode of action of levodopa and GPI-DBS [3,14,22] and show that the two treatment modalities affect temporal and spatial aspects of postural control in different ways. Thus, levodopa had a greater effect on movement 'Start Time' but reduced the spatial accuracy of the leaning task, as shown by the increase in 'Target Overshoot' and 'Wandering' parameters, and increase in 'Target Achievement Time' in the L-DOPA condition. In contrast, GPI-DBS had less of an effect on 'Start Time' but improved the accuracy of the leaning movements, partially reversing the adverse effects of levodopa on 'Target Overshoot' and 'Wandering'. Previous studies concluded that dyskinesias were not the primary cause of the deterioration in postural stability which occurs in the L-DOPA condition [3,14]. In the present study we found that although dyskinesias were only minor or absent at the time of testing, there was a statistical correlation between the dyskinesia rating scale immediately prior to testing and some posturographic measures. It is possible therefore that clinically inapparent dyskinesias may have contributed to the increase in sway and impaired accuracy of the dynamic leaning task in the L-DOPA condition in at least some patients, and that the improvement in these parameters in the DBS+L-DOPA state may have been due in part to suppression of dyskinesias. The observation that these parameters were abnormal even in some patients without any obvious dyskinesias (i.e. an AIMS score of 0) suggests that other factors are probably also involved. The possibility also needs to be considered that dyskinesias may have contributed to the faster 'Start time' in the L-DOPA condition. Further studies of larger numbers of patients with and without dyskinesia are needed to confirm the present findings and to clarify

the contribution of minor dyskinesias to impaired dynamic postural control. Another explanation which has been suggested previously for the increased sway on levodopa is that it is due to reduced tone and stiffness in the postural muscles and to impaired somatosensory feedback [3].

There have been relatively few studies of the effects of GPI-DBS on postural control in IPD and more studies of subthalamic nucleus (STN) stimulation. The preferred target for improvements in PIGD remains unclear [23]. Although some studies have suggested that GPI-DBS is less effective than STN stimulation for axial symptoms [24], a recent randomised double-blind study comparing the outcomes after stimulation at the two sites found that balance confidence and clinical balance scores were superior with GPI-DBS [11]. In addition, a meta-regression analysis of long-term studies suggested that GPI-DBS may provide more sustained benefit in preventing long-term decline in PIGD [10]. The mechanisms by which GPI-DBS improves postural control are uncertain, but it has been suggested that it may be due to descending effects on the pedunculopontine nucleus or other non-dopaminergic centres in the mesencephalic locomotor area [25]. Previous posturographic studies have shown that both GPI and STN stimulation can improve postural sway and balance reactions, including the capacity to respond to postural perturbations [9,14,15], but this was not investigated in the present study. Unlike previous studies which have employed moving platforms to assess postural stability and responses to perturbations, we used a stable balance platform and assessed the speed and accuracy of a whole-body leaning task in which subjects moved their centre of gravity to eccentric positions whilst maintaining a fixed base of support [18]. This test paradigm is particularly pertinent to the maintenance of postural stability during gait initiation in IPD when the ability to maintain

balance in the face of akinesia and freezing is critical to avoid falling, and we have shown previously that it allows discrimination of IPD fallers from non-fallers [18].

Our finding of impaired spatial accuracy and targeting in the whole body dynamic leaning task has some parallels with the ataxia and dysmetria of limb movement that occurs with cerebellar lesions and suggests that there could be a subclinical impairment of cerebellar function in IPD which is aggravated by levodopa and improves with GPI-DBS. While there is no direct evidence for this, it is noteworthy that pathological changes in the cerebellum have been described in IPD, as well as MRI evidence of increased functional activation and connectivity which can be normalised by DBS of the GPI or STN [26]. Moreover, the cerebellum has also been implicated in the pathophysiology of dyskinesias, as well as tremor and other symptoms and as a potential therapeutic target in Parkinson's disease [26]. There are also parallels with the effects of DBS on postural control during other self-initiated movements such as step initiation where, contrary to the effects of L-DOPA, DBS has been shown to impair anticipatory postural adjustments [22].

There are a number of possible limitations to this study. Firstly, although patients were not tested again for 30-60 minutes after DBS was switched off, by which time their typical DBS benefit had worn off, the possibility of some residual effects from the preceding period of DBS cannot be completely ruled out. Secondly, unlike the Control subjects, the IPD patients repeated the posturography test four times and it is possible that the test results may have been influenced by a practice effect, although the randomized sequence of testing was intended to minimise this. The possibility that longer term plasticity effects during the period that the GPI-DBS stimulators were *in situ* may have contributed to the short term responses and interactive effects found in this study also needs to be considered. Lastly, the AIMS scale may be too

insensitive to detect minor dyskinesias and other methods for detection of dyskinesias may need to be considered in future studies.

## **Conclusions**

The results of this study provide further evidence for the differential effects and mode of action of GPI-DBS and levodopa on balance control in longstanding IPD. There appears to be a qualitative deterioration in some aspects of postural control in chronically treated GPI-DBS patients treated with levodopa alone, which GPI-DBS seems to improve. Whether this simply relates to a reduction in axial and limb dyskinetic postural perturbation or alternative hypotheses, such as normalisation of disinhibited cerebellar processes, remains to be determined. Further studies exploring the latter hypothesis could be worthwhile and may lead to novel therapeutic strategies targeted at modulating cerebellar function to enhance motor function and postural control aspects of IPD.

**Conflict of Interest Statement:** None of the authors has any conflicts of interest.

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## Figure Legend

### Figure 1.

(A) Sway Area during stance in IPD patients and the Control subjects. (B) Start Time and Target Achievement Time, (C) Target Overshoot, (D) Wandering for the IPD patients and the Control subjects in the dynamic leaning task. All values are displayed as MEAN $\pm$ SEM. The mean values for the Control subjects are indicated by the dashed lines. (\*) indicates between-group significance of  $p<0.05$  relative to the Control subjects; (†) indicates between-group significance of  $p<0.05$  relative to OFF; (^) indicates between-group significance of  $p<0.05$  relative to DBS; (#) indicates between-group significance of  $p<0.05$  between L-DOPA and DBS+L-DOPA.