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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.

1. 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

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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.

2. Subjects and methods

2.1. Subjects

Ten IPD patients (7 males; mean age 58.8 ± 5.6 years; mean disease duration 13.4 ± 5.8 years; mean Hoehn & Yahr score 2.5 ± 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 ± 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 summarised in Tables 1 and 2. All subjects had bilateral implanted GPI stimulators (mean duration 29.4 ± 15.1 months).

2.2. 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 h. 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 min in all patients. On both days, the patients were first tested with DBS on, then again 30–60 min 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.

2.3. Posturography

Postural measurements were made with patients standing barefoot on a 0.5 m × 0.5 m force platform (AccuswayPlus, Advanced Mechanical Technology, Inc.). Foot position was standardised across assessments by constraining the medial

Table 1
IPD patient demographics. Means and standard deviation unless otherwise stated.

Participant	Gender	Age (years)	Disease duration (years)	Hoehn & Yahr stage (1–5)	Duration of DBS (months)	Medications[#]
1	Male	58	13	3	35	800 mg LED + 2 mg cabergoline
2	Male	54	20	3	60	1500 mg LED + cabergoline 4 mg
3	Male	59	6	2	36	1210 mg LED
4	Male	69	12	2	17	525 mg LED + cabergoline 4 mg
5	Male	60	23	2.5	12	1000 mg LED
6	Female	59	16	2	33	1200 mg LED + cabergoline 6 mg
7	Female	49	8	2	25	500 mg LED + cabergoline 6 mg
8	Male	63	9	3	8	1950 mg LED + pramipexole 1.5 mg
9	Female	54	8	3	29	400 mg LED + cabergoline 3 mg
10	Male	63	19	3	39	800 mg LED
Mean ± SD	7 M/3 F	58.8 ± 5.6	13.4 ± 5.8	2.5 ± 0.5	29.4 ± 15.1	

[#] Total daily doses, levodopa equivalent dose (LED).

Table 2
IPD Patient clinical scores. Means and standard deviation unless otherwise stated.

Participant	UPDRS motor score (0–108)					Tremor score (0–20)				Axial score (0–16)			AIMS Scale (0–28)[*] (DBS on/off)
	OFF	L-DOPA	DBS	DBS + L-DOPA	OFF	L-DOPA	DBS	DBS + L-DOPA	OFF	L-DOPA	DBS	DBS + L-DOPA	
1	28	12	21	10	0	0	0	0	2	2	1	1	1/2
2	37	17	15	13	0	0	0	0	7	2	5	1	2/2
3	47	7	39	5	2	0	2	0	6	0	5	0	0/0
4	30	15	18	15	1	0	0	0	3	2	1	2	0/2
5	37	6	18	4	12	0	4	0	4	0	2	0	1/1
6	22	5	20	4	0	0	0	0	8	0	8	0	3/5
7	32	8	19	3	0	0	0	0	5	6	4	0	4/8
8	36	16	24	11	2	0	1	0	7	2	5	2	5/6
9	34	5	19	4	0	0	0	0	4	0	1	0	1/1
10	36	7	13	4	0	0	0	1	5	1	1	1	0/0
Mean ± SD	33.9 ± 6.6	9.8 ± 4.7	20.6 ± 7.1	7.3 ± 4.4	1.7 ± 3.7	0.0 ± 0.0	0.7 ± 1.3	0.1 ± 0.3	5.1 ± 1.9	1.5 ± 1.8	3.3 ± 2.4	0.7 ± 0.8	1.7/2.7

[*] AIMS (Abnormal Involuntary Movement Scale) scores are based on testing in the L-DOPA condition immediately prior to posturographic assessment.