Postural instability in idiopathic Parkinson’s disease: the role of medication and unilateral pallidotomy

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Summary
Postural instability (PI) is common in idiopathic Parkinson’s disease (IPD). We measured sensory and motor contributions to PI in 50 patients with advanced IPD, off and on medication and in a subset pre- and 3, 6 and 12 months post-unilateral pallidotomy, using computerized dynamic posturography [specifically, the Sensory Organization Test (SOT) and the Unified Parkinson’s Disease Rating Scale (UPDRS) subscale PIGD (Postural Instability and Gait Disorder)]. Off medication, all patients had abnormal PIGD scores. The group could be separated into those with normal SOT equilibrium scores (SOTN) and those, the majority, with abnormal postural control when sensory feedback was limited (SOTABN). Medication improved the PIGD scores but worsened the SOT scores in the majority of patients. Increases in spontaneous sway in some patients contributed to the negative effect of medication on SOT scores. However, this could not explain the detrimental effect of medication on SOT scores in at least 40% of patients. On the other hand, pallidotomy improved both PIGD and SOT scores in both groups. A predictor of good outcome from pallidotomy concerning PI was the degree of worsening of the effect that medication had on SOT5 scores. PI in IPD appears to be multifactorial. We propose that the PIGD score reflects sensory and motor aspects of postural control, with normal sensory feedback, while the SOT equilibrium scores measure the sensory organizational process of postural control in the presence of altered sensory inputs. There is a dissociation between the effects of medication and pallidotomy on motor and sensory components of postural control, which may reflect the underlying pathophysiological mechanism responsible for these different components of PI. We suggest that patients with advanced IPD and PI on medication should consider adjuvant surgical treatment for better postural control.

Keywords: postural control; Parkinson’s disease; medication; surgery; posturography

Abbreviations: COG = centre of gravity; IPD = idiopathic Parkinson’s disease; PI = postural instability; PIGD = postural instability and gait disorder; PPN = pedunculopontine nucleus; SOT = Sensory Organization Test; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction
Postural instability (PI), or impaired balance, is common in idiopathic Parkinson’s disease (IPD), especially as the disease severity advances. Faulty balance mechanisms may contribute to fall-related injuries, restriction of gait patterns and decreased mobility. These disabilities lead to loss of functional independence and social isolation.

The term ‘balance’ refers to a multisystem function that strives to keep the body upright while sitting or standing and while changing posture. Balance is needed to keep the body oriented appropriately while performing voluntary activity, during external perturbations and when the support surface or environment changes.

Horak et al. (1992) proposed that balance (postural stability) requires three distinct processes: (i) sensory organization, in which one or more of the orientational senses (somatosensory, visual and vestibular) are involved and

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integrated within the CNS; (ii) a motor adjustment process involved with executing coordinated and properly scaled neuromuscular responses; and (iii) the background tone of the muscles, through which changes in balance are effected.

Organization of the orientational senses is understood to be an adaptive hierarchical system (Nashner et al., 1982). There are two main reference frames for the sensory representation of the body posture with respect to space (Horak and Macpherson, 1996; Massion, 1998; Mergner and Rosemeier, 1998). On a lower level, a weighted combination of orientational inputs directly mediates the activity of postural muscles and mainly controls the horizontal centre of gravity (COG) position (the bottom-up organization). On a higher level, vestibular inputs provide the orientational reference, against which conflicts in support surface and visual orientation are identified and the combination of inputs adapted to the task conditions (the top-down organization). For postural stability, the information from the lower level must be coherent with the inertial–gravitational reference of the higher level, and any conflicting orientation inputs must be quickly suppressed in favour of those congruent with the internal reference. Thus, in adults, the sensory organizational process is context specific (Nashner et al., 1982; Woollacott et al., 1986) due to the rapid weighting and re-weighting of sensory inputs to/from the lower level by the higher level adaptive process.

Due to the integrated nature of balance and postural stability, a single, objective measure is impossible. Functional measures employed in rehabilitative settings, such as the functional reach and external perturbation tasks (Smithson et al., 1998), serve their purpose well but are less suited to numeric outcome data. Clinical measures of postural control in IPD are derived from items in standardized clinical rating scales, such as the Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn et al., 1987). The commonly accepted Postural Instability and Gait Disorder (PIGD) subscore comprises historical questions relating to falling, walking and freezing, and objective ratings of the patient’s ability to change posture, walk and maintain equilibrium during a retropulsive or propulsive pull (Lozano et al., 1995). The tests that comprise the PIGD score are performed under normal sensory conditions and therefore may weigh more heavily the motor adjustment component of postural control.

Several studies used computerized dynamic posturography to examine the sensory organizational process in IPD (Bronstein et al., 1990; Waterston et al., 1993; Trenkwalder et al., 1995; Toole et al., 1996; Chong et al., 1999), but results were mixed, possibly because of differences in use of medications, conditions tested and analysis techniques.

Many patients with IPD comment that their ‘balance’ seems worse on medication. Proposed aetiologies for this have assumed that medication-induced increases in mobility combine with disease-related, slower reaction times to reduce postural stability. The result implied is that patients on medication are more likely to sway beyond their limit for maintenance of an upright stance and are then more likely to be unable to right themselves in time before losing balance.

Surgical treatment of IPD is now widely pursued in advanced disease stages when the effectiveness of medication is reduced by motor response complications, such as dyskinesias and unpredictable and fluctuating motor states. The resurgence of surgical treatment for Parkinson’s disease in the 1990s began with ablative treatment, such as pallidotomy. Although the technology has turned to deep brain stimulation, carefully placed unilateral pallidal lesions have been found to be a successful adjuvant treatment in advanced Parkinson’s disease. Most studies of unilateral pallidotomy, which have assessed outcomes at ≥6 months postoperatively, reported sustained improvements of ≥25% in motor control scores as measured by the motor subscore of the UPDRS-III (Svensnilson et al., 1960; Laitinen et al., 1992; Dogali et al., 1995; Lozano et al., 1995; Baron et al., 1996; Fazzini et al., 1997; Kishore et al., 1997; Lang et al., 1997; Giller et al., 1998; Masterman et al., 1998; Samuel et al., 1998; Scott et al., 1998; Shannon et al., 1998; Baron et al., 2000; Fine et al., 2000).

In contrast to motor control, the impact of pallidotomy on PI has been hard to assess. About half of the studies reporting long-term clinical outcomes of pallidotomy commented specifically on postural control. The measurement of postural control varied from qualitative comments to a single measure of postural control, the retropulsion score from the UPDRS-III (Fahn et al., 1987), to a subscore, the PIGD score (Lozano et al., 1995). Long-term improvement in postural control generally was not seen.

Our overall goal was to understand the effect of therapeutic interventions such as medication and/or surgery on PI in IPD. We employed clinical measures of PI from the UPDRS and measures of the sensory organizational process of postural control using computerized dynamic posturography to address these questions: what is the nature of PI in a group of patients with moderate to advanced IPD? Is PI due to abnormalities of the sensory organizational process, abnormal function of the motor adjustment process and the background muscle tone, or is it due to a breakdown in the hierarchical process and deficiencies in sensorimotor integration? Are there different types of PI within this group of IPD patients? What roles do medication and surgery play? Here we report the effects of medication and unilateral pallidotomy. Our findings after bilateral subthalamic deep brain stimulation are the subject of a separate study.

Subjects and methods

Subjects

Fifty patients with IPD without dementia, clinical signs of vestibular disease, weakness or peripheral sensory loss consented to participate in a study of postural stability using computerized dynamic posturography, in addition to the standard UPDRS, in accordance with the Declaration of
Helsinki. The study was approved by the Stanford University Medical Center Ethics Committee. Table 1 shows the demographics of the patients as a group.

Patients were studied in their best on-medication state and in the practically defined off-medication state. Long-acting dopaminergic medications [Sinemet-CR (DuPont Pharma Inc.) and dopamine agonists] were withdrawn 24 h in advance and short-acting medications were withdrawn at least 12 h in advance of the off state testing. A subset of 10 patients was also studied using the CAPIT (Core Assessment Program for Intracerebral Transplantation) (Langston et al., 1992) pre- and 3, 6 and 12 months post-unilateral pallidotomy. Inclusion criteria for pallidotomy required that the patient have levodopa-responsive IPD, at Hoehn and Yahr stage III or greater off medication, have failed optimum medical therapy for at least 4 weeks, have no evidence of dementia and have no severe atrophy on MRI.

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<th>Table 1 Patient demographics, n = 50</th>
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<td>Mean ± SD (range) or median (25th, 75th percentile)</td>
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<td>Age (years)</td>
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Clinical assessment
All patients were evaluated with the UPDRS and in a study of postural sway in altered sensory conditions using computerized dynamic posturography. The PIGD score was calculated by adding items 13, 14, 15, 29 and 30 (falling, freezing, gait and postural stability) from the motor and activities of daily living portions of the UPDRS, to represent clinical mobility. The dyskinesia intensity score was item 32 of the UPDRS.

Computerized dynamic posturography
Computerized dynamic posturography is a quantitative method for assessing upright balance function under a variety of conditions that simulate conditions encountered in daily life (Nashner, 2001). Subjects stand on moveable forceplates in a loosely fitting harness. Their feet are carefully aligned over defined axes on the forceplates, which are referenced to the four force transducers mounted on a supporting centre plate. Forceplate technology measures vertical forces imposed by the upright subject (Nashner, 1993). These measures along with the height and the weight of the patient are used to calculate the the COG angle. In computerized dynamic posturography, the change in the COG angle is measured in real time and is called COG sway. The four conditions of the Sensory Organization Test (SOT) are designed to assess the patient’s ability to use and integrate somatosensory, visual and vestibular inputs effectively to maintain balance and therefore not to sway excessively. Sensory organization is evaluated by selectively disrupting somatosensory and/or visual information regarding the body’s COG in relation to the vertical and then measuring the patient’s ability to maintain balance. Continuous measurements are made of the COG sway, but the equilibrium score (see below) reflects the maximum AP (anterior–posterior) COG angle measured per trial as a percentage of the theoretical, maximum sway a normal subject can tolerate before losing balance. The larger the COG angle, the more the subject swayed and therefore the lower the equilibrium score. Measurements of SOT over time have been shown to be consistent within 5% and unaffected by a learning bias (Coogler and Wolf, 1992; Nashner, 1993; Paloski et al., 1999).

In the SOT, the subjects stood quietly for 20 s trials on moveable forceplates (Smart EquiTest, NeuroCom, Clackamas, OR, USA). All patients looked straight ahead with their head vertically aligned with respect to the axis of the trunk; no patient had obvious antero-, latero- or torticollis. The subject’s performance was recorded during three trials in each of the four conditions shown in Fig. 1. In SOT1, all sensory inputs were available for orientation; subjects stood with their eyes open and somatosensory information was available from the fixed platform. Measurements in this condition reflected spontaneous postural sway. In SOT2, visual information was eliminated by asking the subjects to close their eyes. In SOT4, somatosensory information was made inadequate for orientation by rotation of the platform about the ankle joint axis in proportion to spontaneous AP sway. In SOT5, somatosensory and visual inputs were made unavailable due to the rotation of the platform with the subject’s eyes closed.

The equilibrium score compares the subject’s sway with theoretical limits of stability. The theoretical maximum displacement a normal subject may sway without losing balance is assumed to be 12.5° (8.25° anterior, 4.25° posterior; McCollum, 1989). The equilibrium score = [12.5 – θ (max–min)/12.5] × 100%, where θ is the maximum AP COG sway angle recorded per trial; see above. The equilibrium score for each condition reflects the average score for the three trials. A fall is registered when subjects take a step or require assistance by the test administrator. A fall is given a score of zero.

Equilibrium scores in clinically normal subjects
The normative data used in this study have been reported elsewhere (Nashner, 1993) and comprise data from 194 normal subjects in three age groups; between 20 and 59 years, between 60 and 69 years and between 70 and 79 years. Clinically abnormal scores in SOT are taken as those that are worse than 95% of the clinically asymptomatic control sample.
A number of other studies have reported asymptomatic normative data for SOT, which are in agreement with the normative data used in this study (Horak et al., 1989; Peterka and Black, 1990; Beckley et al., 1991; Wolfson et al., 1992). The fifth percentile normative data, weighted for our patients’ age group range, were: SOT1 = 87%, SOT2 = 82%, SOT4 = 73% and SOT5 = 50%. For each SOT score, this was calculated by multiplying the established fifth percentile values for each of the three age groups by the fraction of the total number of patients in that group and adding the three values. In this study, the patients’ equilibrium score for each condition was compared with the fifth percentile of age-based normative data. A score below the weighted fifth percentile was considered abnormal.

**Surgical technique**

Patients underwent stereotactic, microelectrode-guided pallidotomy. Medication was withheld for at least 12 h before the procedure. Identification of the sensorimotor region in globus pallidus internus (GPI) employed multipass, single neuronal, microelectrode recording and followed the anatomical sagittal sections from the Schaltenbrand and Bailey Atlas (Schaltenbrand and Bailey, 1959) and the somatotopic map of the GPI developed by DeLong et al. (unpublished observation) at Emory University. Radio frequency lesions were made by sequential heating of the macroprobe (1 mm diameter whose last 3 mm were uninsulated) (Radionics Inc., Burlington, MA, USA). Constant examination of the patient’s speech, vision and motor function throughout lesion making confirmed the lack of capsular or optic tract encroachment. Lesions were made in three passes in two planes to conform to the mapped volume of the sensorimotor region. Lesion location and size were determined from immediate postoperative MRI scans taken <3 days postoperatively.

**Statistical analysis**

The Student’s \( t \) test indicates the magnitudes of the differences of means and therefore the magnitude of the observation. Thus, the unpaired \( t \) test was used to assess the difference between SOT scores of the IPD patients and those of normal subjects. The paired Student’s \( t \) test was used to assess the statistical significance of differences in the mean of SOT scores off and on medication. The paired Student’s \( t \) test was also used to assess the statistical significance of differences in the mean of the SOT1 score pre- and post-pallidotomy on medication, and SOT5 score pre- and post-pallidotomy off medication. All tests were two-tailed. For non-parametric data (PIGD and all other clinical rating scale scores), the Wilcoxon signed rank test was used to determine the significance of the treatment on the appropriate measures. Spearman rank correlation and/or the Mann–Whitney rank sum test were used to assess the relationship between PIGD score off and on medication, PIGD scores and SOT5 scores, dyskinesia scores and SOT1 and SOT5, the relationship of the change in PIGD due to pallidotomy or the change in PIGD due to medication and preoperative SOT5 score on medication. Spearman rank correlation was also used to assess the relationship between groups as regards their Hoehn and Yahr stage, UPDRS motor subscores and change in UPDRS scores due to medication. A \( P \) value of \( \leq 0.05 \) was used as the level of significance. A Bonferroni correction was not indicated as these were tests of multiple single comparisons rather than multiple comparisons of a single outcome.

**Results**

Patients off medication maintained equilibrium within the normal range under conditions SOT1 and SOT2 (Fig. 2).
However, the mean SOT4 score averaged slightly below the lower limit of normal, and the SOT5 score was significantly below normal. More specifically, 52% of the patients exhibited greater postural sway than 95% of normal subjects in condition SOT5 while off medication, the condition during which both somatosensory and visual inputs were disrupted. Patients were divided into two groups: those with SOT5 equilibrium scores in the normal range (SOTN group) and those with SOT5 scores below the fifth percentile of the normal subject data (SOTABN group) (see Fig. 3A and B). Apart from one patient, this separation divided the group into those with normal scores for all SOT conditions and those where either SOT4 and/or SOT5 were abnormal. Interestingly, the two groups were very similar in age, and duration and severity of disease, as shown in Table 2. SOT5 scores did not correlate with the patients’ medication-induced changes in their UPDRS scores, showing that having lower SOT5 scores was not suggestive of atypical Parkinsonism.

Figure 3A and B compares SOT scores off and on medication for the SOTN and SOTABN groups, respectively. Scores of the SOTN group on medication decreased from their normal off-medication values, representing loss of postural stability under all conditions (Fig. 3A). Decreases in SOT1, SOT2 and SOT4 scores averaged between 5.4 and 7.9%, while SOT5 scores decreased by a larger average of 16.3%. On equilibrium scores were significantly lower than off scores in SOT1, SOT2 and SOT5.

The SOTABN group had SOT4 and SOT5 scores, off medication, that were significantly below normal ($P < 0.002$, Fig. 3B). In the on-medication state, the decreases in their SOT1 and SOT2 scores compared with the scores in the off-medication state were similar to those of the SOTN group, averaging 4.4 and 6.0%, respectively. SOT4 scores decreased by an average of 6.4% on medication. Medication-induced changes in SOT5 were more difficult to assess, as many of them fell repeatedly both off and on medication, and the SOT5 score was very low (group average = 17%, normal >50%), suggesting that these patients developed PI when they did not have adequate somatosensory and/or visual feedback and were much more unstable without either. The variance in SOT4 and SOT5 was due partially to the presence of falls (equilibrium score = 0) in some patients in each condition. Although the SOT5 score decreased on medication in the SOTN group, the mean for that group was still significantly higher than that of the SOTABN group on medication ($P < 0.001$).

The effect of medication on the SOT5 performance of all patients is summarized in Fig. 4, which compares on- and off-medication scores on an $x$–$y$ plot. Seventy per cent of the patients had abnormal SOT5 scores on medication. As evidenced by points in the lower left quadrant, 40% of patients had abnormal SOT5 scores both off and on medication, and PI was severe enough in seven patients to produce falls on every SOT5 trial, off and on medication (represented
by one data point). Thirty per cent of the patients performed within normal limits off medication but became abnormal on medication (lower right quadrant). Only 12% of patients were abnormal off medication and then improved performance to normal on medication (upper left quadrant). Finally, 18% of the patients performed normally both off and on medication (upper right quadrant), with most of these points clustering near the diagonal line, indicating little if any change with medication.

The overall effect of medication on SOT5 performance can be seen by comparing points above and left with those below and right of the diagonal 'no change' line. Locations representing no changes between the on and off medication scores fall along the dashed diagonal line, slope = 1.

The overall effect of medication on SOT5 performance can be seen by comparing points above and left with those below and right of the diagonal ‘no change’ line. Excluding points falling within \( \pm 5\% \) of the line, 66% of the patients were less stable on compared with off medication. Thus the predominant effect of dopaminergic medication was to decrease SOT5 equilibrium scores.

We used the standard UPDRS subscale, PIGD, to investigate the effect of medication on a clinical measure of postural control. The PIGD score of all except three patients’ improved on medication. The SOTABN group tended to show less improvement in PIGD due to medication than the SOTN group and behaved more homogeneously in this regard (\( r = 0.72 \) for the SOTABN group versus \( r = 0.47 \) for the SOTN group; data not shown). However, this difference did not reach statistical significance.

SOT5 scores were not correlated with the PIGD score or any component of the PIGD score, off medication (data not shown), suggesting that SOT5 and PIGD are measuring different components of postural control. We noted that all patients had abnormal PIGD scores and that some of the patients with the highest PIGD scores had normal SOT5 scores. There was also no correlation between the change in SOT5 and the change in PIGD with medication. This was not surprising as the overall effect of medication was to improve the PIGD score but to make the SOT5 score worse.

To evaluate the hypothesis that decreases in SOT5 on medication are purely a function of increased spontaneous sway (i.e. decreased SOT1 scores), we compared on and off medication changes in SOT5 and SOT1 scores (Fig. 5). Medication made most patients worse in both SOT1 and SOT5, as most data points fell into the third quadrant. There were essentially two categories of responses within this quadrant: those with large decreases in SOT1 scores, in the region of 20%, and those whose data points were close to the vertical axis indicating no changes in SOT1. Among patients with large decreases in SOT1, none showed improvement in SOT5, demonstrating that the effect of increased spontaneous sway, on medication, was also deleterious to postural stability in SOT5. In Fig. 3A and B, decreases in SOT1 and SOT4 scores on medication were similar in magnitude, suggesting that, on average, mechanical effects of platform motion under SOT4 did not tend to amplify the spontaneous sway. If we applied the same assumption to SOT5 scores on medication, we could then attribute decreases in SOT5 scores on medication to spontaneous sway only when the SOT5 decreases were less than or equal to SOT1 decreases. Under this assumption, increased spontaneous sway explained the on-medication deterioration of SOT5 scores in 10% of patients, while there appeared to be additive deteriorations in SOT5 scores in 40% of the patients that were not explainable solely by the spontaneous sway effect.

Abnormal spontaneous postural sway, corresponding to a low SOT1 equilibrium score, was only seen in the on-medication state and may have been due to dyskinesias. Using the dyskinesia intensity score of the UPDRS, we examined whether there was any correlation between

| Table 2 Mean (±SD) or median (25th, 75th percentiles) values for SOTN and SOTABN groups |
|--------------------------------|--------------------------------|
| Age (years) | 59.5 ± 8.0 | 61.2 ± 10.7 |
| Duration of illness (years) | 12.1 ± 4.9 | 11.5 ± 4.7 |
| Hoehn and Yahr stage, off | 3 (3, 3) | 3 (3, 4) |
| UPDRS motor score, off | 35.5 (30, 40) | 39 (31, 47) |
| Change in UPDRS motor score, off to on | 15 (10, 23.3) | 19 (5.3, 30.5) |

\( P \text{ value} \)
dyskinesia severity scale and the change in SOT1 and/or the change in SOT5 due to medication. Figure 6A and B shows that there was a more significant correlation between dyskinesias and the change in SOT1 than with the change in SOT5, suggesting that dyskinesias had more effect on the SOT1 than the SOT5 equilibrium scores.

The effect of pallidotomy on postural instability

Figure 7 shows the SOT1 equilibrium score pre- and 3, 6 and 12 months post-pallidotomy, off and on medication for the group of surgical patients. Post-pallidotomy, there was a non-significant improvement in the already normal SOT1 scores, off medication. There was a more noticeable improvement in the SOT1 scores on medication that was significant at 6 months ($P = 0.01$) and was close to being significant at 3 and 12 months postoperatively ($P = 0.08$ and $P = 0.07$, respectively). Pallidotomy also improved the on scores in SOT2 and SOT4, bringing them closer to the off scores (data not shown).

We divided the surgical patients into the same two groups based on preoperative off-medication SOT5 scores, those with normal scores (SOTN; $n = 4$) and those with abnormal scores (SOTABN; $n = 6$). We then analysed the effects of unilateral pallidotomy on the separate groups.

Figure 8A and B demonstrates the effect of pallidotomy on the SOT5 scores of each group. Pallidotomy improved the already normal SOT5 scores off medication in the SOTN group (Fig. 8A), and brought the abnormal SOT5 scores on medication into the normal range. Thus, unilateral pallidotomy reduced but did not abolish the detrimental effect of medication on SOT5 scores. Figure 8B shows that, in patients with SOTABN scores, pallidotomy improved the off medication SOT5 scores significantly, bringing the mean SOT5 scores, both off and on medication, into the normal range. This significant effect was maintained at 6 and 12 months.

Both groups showed improvement in the PIGD score 3 and 6 months after pallidotomy. The improvement for the SOTABN group appeared more robust and was maintained over 12 months. Preoperatively, the average PIGD score of the two groups was similar, off medication (PIGD = 7.3 for SOTN and 7.8 for SOTABN). Post-pallidotomy, the SOTABN group improved by 57% at 3 months, which declined only slightly to 42% at 12 months. In contrast, improvements in the SOTN group were smaller at 3 months (37%) and were almost completely lost by 12 months (2%). The sample size was small, however, and this difference did not reach significance. The improvement in PIGD scores from unilateral pallidotomy was correlated with the improvement in SOT5 scores, off medication, especially in the SOTABN group (data not shown, $r = 0.77$, 0.82 and 0.86 at 3, 6 and 12 months, respectively). Thus, it appeared that the patients with the SOTABN scores off medication, pre-pallidotomy, tended to gain more improvement from pallidotomy, in terms of both their SOT5 scores and their PIGD scores, than the SOTN group.

Figure 9A shows the effect of pallidotomy on the PIGD score off medication as a function of preoperative SOT5 scores on medication, 3, 6 and 12 months after surgery. This shows an inverse correlation between the improvement in PIGD from pallidotomy and the SOT5 score on medication, i.e. a low SOT5 score on medication predicted better clinical mobility improvement from pallidotomy. In contrast, the effect of medication on the PIGD score 3, 6 and 12 months post-pallidotomy was greater the higher the SOT5 score preoperatively on medication (Fig. 9B).

Discussion

We have found that in a group of 50 patients with advanced IPD, there are two distinct off-medication SOT5 scores on medication, 3, 6 and 12 months after surgery. This shows an inverse correlation between the improvement in PIGD from pallidotomy and the SOT5 score on medication, i.e. a low SOT5 score on medication predicted better clinical mobility improvement from pallidotomy. In contrast, the effect of medication on the PIGD score 3, 6 and 12 months post-pallidotomy was greater the higher the SOT5 score preoperatively on medication (Fig. 9B).

The aetiology of abnormal SOT5 equilibrium scores in IPD

All patients demonstrated postural stability when somatosensory information was available in addition to vestibular sensory information. This agrees with other studies of PI in
patients with IPD (Horak et al., 1992). Patients with bilateral vestibular disease fall repeatedly under SOT5 but typically do not under the other SOT conditions (Nashner et al., 1982). In conditions SOT4 and SOT5, there is almost no somatosensory feedback from the ankle proprioceptors, but some somatosensory feedback from other gravireceptors located in the kidney and large vessels remains intact (Mittelstaedt, 1996; Dietz, 1998). This suggests that in SOT5 there is only a small amount of sensory input available to use for the control of posture other than vestibular sensory information.

Based on the above arguments, abnormal SOT5 scores in Parkinson’s disease suggest that (i) postural control centres are not receiving any vestibular information due to peripheral or brainstem dysfunction; (ii) that there is a specific deficit in vestibular, sensorimotor integration within the postural control centres; or (iii) that the interactions between the higher and lower hierarchical processes of postural control are deficient.

We do not believe that deficits in SOT5 can be explained by peripheral or brainstem vestibular disease in our group, as none of these patients had clinical signs of vestibular disease; there was no nystagmus and the VOR (vestibular ocular reflex) was normal as measured by clinical exam. This conclusion agrees with the results of other in-depth studies of vestibular function in IPD (Pastor et al., 1993; Bronstein et al., 1996). However, in a study of 36 patients with IPD of varying severity, Reichert et al. (1982) reported that 31% had absent calorics responses, consistent with bilateral peripheral and/or central vestibular dysfunction. Waterston et al. (1993) found deficits in SOT5 in patients with more advanced IPD, only two of whom had vestibular dysfunction as measured by calorics. They concluded that the main pathology related to the motor system.

If peripheral vestibular sensory inputs are normal in IPD, then another logical explanation for the prevalence of abnormal SOT5 equilibrium scores would be specific deficits in central vestibular, sensorimotor integration, as proposed by Martin (1967). Although this may be a partial explanation, we do not think that the SOTABN patients only had a specific deficit in vestibular, sensorimotor integration because they also demonstrated reduced postural stability in condition SOT4, when both vision and vestibular information are available for postural control.

We propose that the deficits in the sensory organizational process in IPD reflect a breakdown in the central hierarchy of postural control. We suggest that in the majority of our patients, the higher reference system for postural control can no longer ‘automatically’ enable the desired lower level synergies to maintain equilibrium without coincident, coherent sensory feedback. This is similar to Horak’s proposal that deficits in different sensory conditions reflect an inflexibility in the ability of IPD patients to adapt to altered support conditions (Horak et al., 1992). Demirci et al. (1997) have proposed that patients with Parkinson’s disease underestimate somatosensory feedback (‘kinaesthæsia’) when estimating
the amplitude of passive angular displacements of the finger. Thus, in SOT5, although there is probably still some gravireceptor feedback present, patients with IPD may be unable to use this adequately to maintain balance.

Contrary to the data from normal subjects, we did not identify a specific ‘visually dependent’ group of IPD patients as regards their sensory organizational control of posture (Isableu, 1997). However, this was not possible with the SOT conditions available. The measurement of visual dependence can be achieved using SOT by comparing equilibrium in conditions of visual absence with conditions where visual feedback is incongruent. Visually dependent subjects continue to use visual cues for postural control even if they are inappropriate (Nashner, 1993). Dietz and others have proposed that patients with Parkinson’s disease rely extensively on vision and flexor muscle control for balance control during stance and locomotion (Dietz, 1998; Azulay et al., 1999). They hypothesize that extensor load receptors act as body graviceptors and are related mainly to balance on the basis of a ground reference frame. They propose that in Parkinson’s disease these receptors are poorly functioning, leaving the patient dependent on vision. As there was no marked deviation of the vertical orientation of the head, our data suggest that the ground-based reference frame still played an important role in postural control in all our Parkinson’s disease patients as their equilibrium was normal until this was made unavailable (conditions SOT4 and SOT5).

Bernstein (1967) proposed that the nervous system organizes movement in a hierarchical manner. Higher levels activate lower level synergies, which are groups of muscles acting as a unit. The higher levels then are more concerned with adapting ‘motor’ responses to alterations in task or environmental conditions. Marsden hypothesized that a major role for the basal ganglia in motor control is the ‘automatic execution of learned motor plans’, suggesting a role for the basal ganglia in the higher level of a hierarchical structure (Marsden, 1982).

Anatomical evidence suggests that such a postural reference system exists, mediated by the motor cortex, caudate nucleus and brainstem locomotor regions such as the pedunculopontine nucleus (PPN) (Garcia-Rill et al., 1985). Visual and vestibular inputs to the motor cortex, and the
The effect of dopaminergic medication on postural control

Dopaminergic medication improved the PIGD score in all but three patients. On the other hand, medication worsened SOT5 scores in 66% of the patient group. In at least 40% of the patients, the decreases in SOT5 equilibrium scores, on medication, could not be explained only on the basis of the decrease seen in SOT1.

A decrease in the SOT1 score reflects increased spontaneous sway. Why might this occur in IPD? Horak et al. have proposed that increases in spontaneous sway in response to external perturbations in IPD patients, on medication, are due to decreases in muscle tone without increases in corrective EMG burst amplitudes (Hallett and Khoshbin, 1980; Horak et al., 1996). However, there is no external perturbation in the condition SOT1, as this is the ‘baseline’ condition, when all sensory inputs are available for postural control. Another explanation for the increased spontaneous sway was the presence of dyskinesias. The decrease in SOT1 was correlated with the severity of dyskinesia. One would expect the presence of spontaneous sway to affect the other sensory conditions. In fact, SOT1, SOT2 and SOT4 decreases on medication were similar. However, there were relatively larger decreases in SOT5 scores on medication. We could only explain the decrease in postural stability in SOT5, purely from the decrease in SOT1 in 10% of patients, while there appeared to be an additional detrimental effect of dopaminergic medication in as many as 40% of the patient group when both somatosensory and visual information were unavailable for the control of equilibrium. We propose a mechanism for this effect in the final section of the paper.

The effects of pallidotomy on the motor and sensory components of postural control

In contrast to the effects of medication, unilateral pallidotomy resulted in substantial improvements in both the SOT5 equilibrium score and the PIGD score. Both the SOTN and SOTABN groups demonstrated improvements in SOT5, but the improvements were especially significant in patients with abnormal SOT5 scores preoperatively, off medication. In these patients, SOT5 scores were brought into the normal range following pallidotomy and remained so over the 12 months of follow-up. The PIGD score improvements also tended to be greater and more sustained in the SOTABN group after pallidotomy.

Out of 24 studies reporting pallidotomy outcomes, 12 included postural control (Iacono et al., 1995; Lozano et al., 1995; Baron et al., 1996; Johansson et al., 1997; Kishore et al., 1997; Lang et al., 1997; Masterman et al., 1998; Samuel et al., 1998; Melnick et al., 1999; Baron et al., 2000; Fine et al., 2000). Among these 12 studies, eight reported on clinical measures of postural stability using subscores from the UPDRS; three from the same centre (Lozano et al., 1995; Lang et al., 1997; Fine et al., 2000) used the PIGD score, the
remainder used the single postural stability score from item 30 of the UPDRS motor scale (Fahn et al., 1987). Three reported measures of postural control using posturography. Only one of 12 studies reported no early improvement in postural control (Melnick et al., 1999). Although the other studies reported early improvements, none saw long-term benefit of unilateral pallidotomy on postural control. Sustained improvements were seen in individual patients in one long-term study (Vitek et al., 2000).

Had we combined the two groups in our study, we too might have seen an overall decline in PIGD improvement by 12 months. However, by separating patients based on presurgical SOT5 results, we found that improvements in PIGD scores in the SOTABN group declined only slightly from 57% at 3 months to 42% at 12 months. In contrast, improvements in the SOTN group were smaller at 3 months (37%) and were almost completely lost by 12 months (2%). Our patient group is small and we have not reported here the correlation of overall outcome with lesion location, which might also have influenced these findings (Bronte-Stewart et al., 1998).

Our findings concerning the effect of pallidotomy on the sensory organizational process in IPD are in agreement with two other studies, which also showed improvement in the equivalent of all of the SOT scores. One of these was performed in the on-medication state only (Masterman et al., 1998). The other showed significant improvement in a combined score of SOT4, 5 and 6, in the off-medication state postoperatively, but testing was done only between 1 and 3 months postoperatively (Mandybur et al., 1999). Our results are not easy to compare with the third study that used posturography. This study showed no significant efficacy at 3 months (Melnick et al., 1999), but the composite SOT score was used rather than the scores of the individual sensory conditions, and all patients were treated as one group.

**Are there different treatment strategies for the two groups of patients?**

It appears that patients with IPD and PI have different presentations of PI. One might classify them as patients with more significant difficulties with movement initiation and velocity features and those with additional impairment of the sensory organizational component of postural control. For the first time, we have found that there was a dissociation between the effects of medication and the effects of pallidotomy on the motor and sensory aspects of postural control. Medication clearly improved the motor adjustment component of postural control but could be detrimental to the sensory organizational control of posture. Pallidotomy, on the other hand, could completely correct abnormalities in the sensory organizational component of postural control as well as improve the motor components of balance and mobility. It appeared that the patients whose SOT5 scores were the worst on medication stood to gain the most improvement in PIGD scores from pallidotomy. Those with normal or above normal SOT5 scores, however, still gained improvement in PIGD from medication, post-pallidotomy.

Thus, patients with IPD, PI and abnormal SOT5 scores would appear to be good candidates for surgery, if PI is a disabling symptom. For patients with IPD, PI and normal SOT5 scores, we suggest that the PI of these patients can be treated adequately with medication alone and that the decision to undergo surgery should be made for other reasons, such as motor fluctuations and a narrow therapeutic window. The most appropriate measurement to predict management strategy was the preoperative SOT5 equilibrium score, on medication.

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**Mechanisms for the different effects of medication and surgery on the motor and sensory components of postural control**

The basal ganglia are part of multiple segregated circuits that mediate motor, oculomotor, limbic and associative functions. Anatomical and physiological evidence suggests that the striatum is a site of spatio-temporal, context-dependent, sensorimotor integration, which is directly influenced by dopamine (Flaherty and Graybiel, 1991, 1993, 1994; Graybiel et al., 1994; Mink, 1996). Inhibitory output signals travel from Gpi to the thalamus and from there are returned to the premotor cortex. Gpi also directly inhibits brainstem targets and the PPN in particular (Garcia-Rill, 1991; Parent and Hazrati, 1995a, b; Winn et al., 1997; Dormont et al., 1998). The PPN appears to be part of a parallel basal ganglia pathway with dense reciprocal connections with the subthalamic nucleus and with extensive output to the thalamus. The PPN appears to be integral to postural control and locomotion (Garcia-Rill, 1986; Conde et al., 1998), and it has been proposed that the PPN may play an important role in conditioned sensorimotor performance (Dormont et al., 1998).

In IPD, abnormal physiology is encountered in the basal ganglia. In Gpi neurones, the mean discharge rates increase and firing patterns become abnormally irregular with increased bursting activity and synchronization (Filion, 1979; Miller and DeLong, 1987, 1988; Vitek et al., 1990, 1994; Nini et al., 1995; Feingold et al., 1996; Raz et al., 1997). Vitek and Giroux (2000) have proposed that the changes in the firing patterns and degree of synchronization in the basal ganglia interfere with downstream signal transmission and disrupt normal spatio-temporal patterns of subcortical and cortical neuronal activity. Increased oscillatory firing patterns are also seen in hyperkinetic states (Suarez et al., 1997), and Vitek and Giroux (2000) have proposed that dyskinesias in Parkinson’s disease may be partially related to irregular firing patterns in basal ganglia neurones. Dopaminergic medication has been shown to reduce firing rates in Gpi to normal, but medication may cause further bursting and irregularity in firing patterns (Filion et al., 1991;
Merello et al., 1999). Medication also contributes to dyskinesias.

Pallidotomy reduces the inhibitory effects on the thalamus by reducing pallidal neuronal firing rates. Contrary to the effect of medication on firing patterns, pallidotomy may normalize firing patterns in pallido-thalamocortical and pallido-PPN-thalamocortical pathways (Vitek and Giroux, 2000).

Thus, at least two possible mechanisms exist for the different effect of dopaminergic medication and pallidotomy on the motor and sensory organizational processes of postural control. First, there are different sites for spatio-temporal, context-specific, sensorimotor integration: the striatum for appendicular motor control and the PPN for axial motor control, i.e. postural control and locomotion. Dopamine may facilitate sensorimotor integration in the striatum but does not influence the PPN. Pallidotomy would affect largely sensorimotor integration in the PPN. This leaves unexplained how dopamine could impair the sensory organizational process. Secondly, we propose a different reason for the differing effects of medication and surgery on the different clinical aspects of the disease, which may be linked to the pathophysiological changes in the basal ganglia. This is illustrated in a Venn diagram (Fig. 10).

The motor adjustment component of motor and postural control may be mediated mainly by changes in the tonic firing rates of GPi neurones, reflected in downstream targets. The sensory organizational process may depend more on coherent firing patterns. Medication and pallidotomy reduce firing rates, thereby releasing downstream nuclei from the inhibition and improving motor function. This has been proposed as the mechanism for the improvement in rigidity, bradykinesia and we suggest for the motor aspects of postural control from medication and post-pallidotomy. Medication can make irregular firing patterns worse, and pallidotomy can improve them. This may explain why medication worsens but pallidotomy improves the sensory aspects of postural control. Thus, the same pathophysiological process might underlie medication-induced dyskinesias and the effect of medication on the sensory organizational process of postural control. The worsening of SOT5 on medication may be partly due to motor effects of dyskinesias supplemented by even further disruption of sensorimotor information processing. This would explain the dissociation between the effects of medication and pallidotomy on the motor and sensory aspects of PI in Parkinson’s disease. We currently are studying the same effect after deep brain stimulation in the subthalamic nucleus in Parkinson’s disease.

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**References**


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