Effect of chronic bilateral subthalamic nucleus (STN) stimulation on postural control in Parkinson's disease

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Summary

Postural instability is one of the most incapacitating factors in Parkinson's disease (PD). The underlying deficits and the effects of treatment are still not well understood. The aims of the present study were: (i) to identify abnormalities of postural control in PD patients during unperturbed stance and externally perturbed stance (anterior–posterior tilts of the support surface and of the visual scene); (ii) to assess the effects of L-dopa medication and subthalamic nucleus (STN) stimulation on posture control; and (iii) to characterize potential differential or additive effects of both treatments. Eight PD patients under chronic STN stimulation were investigated and compared with 10 normal controls. The assessment was performed in a crossover design (± STN stimulation, ± L-dopa). During unperturbed stance, we recorded measures of spontaneous sway in terms of displacement, velocity and frequency of the centre of pressure (COP), lower body (LB) and upper body (UB) excursions. In addition, inter-segmental UB–LB coupling was investigated as a measure of axial stiffness. All these measures were abnormally large in patients OFF treatment. Under L-dopa treatment, the velocity, frequency and coupling measures were reduced, whereas sway amplitude increased. Very similar effects were obtained under STN stimulation, and these effects became more pronounced in the combined treatment condition. In these data, reduction of inter-segmental coupling correlated with increase in sway amplitude. The finding suggests that axial stiffness reduction under treatment revealed a treatment-resistant deficit in the sensorimotor postural control loop. However, these two effects did not correlate with the motor subscores of the unified Parkinson's disease rating scale (UPDRS), which indicates that they are of minor functional relevance for posture control. A frequency peak in the COP excursions at 0.7–1.1 Hz, which we take to indicate a resonance behaviour of the postural control loop, became reduced under therapy. The reduction of this peak did correlate with most improvements in the UPDRS under therapy. Support surface tilt revealed that an UB righting on the LB segment, which is present in normal controls, is missing in the patients. The postural responses to visual tilt were abnormally large in patients, independent of whether the support was stable or slightly moving, while the control subjects clearly profited from a stable support. This finding suggests that PD patients lack the ability of normal subjects to use sensory or cognitive information when suppressing the destabilizing effect of visual tilt. These abnormal tilt reactions of the patients were resistant to treatment with L-dopa, STN stimulation and a combination of the two. Overall, the effects of STN stimulation on posture control essentially paralleled those of L-dopa during both unperturbed and externally perturbed stance.

Keywords: Parkinson's disease; posture control; movement disorders; STN stimulation

Abbreviations: COP = centre of pressure; GPI = globus pallidum internus; LB = lower body; PD = Parkinson's disease; PSD = power spectral density; RMS = root mean square; STN = subthalamic nucleus; UB = upper body; UPDRS = unified Parkinson's disease rating scale

Introduction

Postural instability is a severe problem in patients with Parkinson's disease (PD), often leading to falls and injuries (Wood *et al.*, 2002). The problem becomes accentuated with progression of the disease. Numerous studies have been devoted to identifying the underlying pathophysiology of the instability, revealing several impaired functions related to posture control such as inappropriate responses to external stimuli, an insufficient central scaling of postural muscle tone, deficits in postural synergies and an inability to adjust the postural patterns to the behavioural context (Marsden, 1982; Alexander and Crutcher, 1990; Hallett, 1993; Horak *et al.*, 1996).

The postural instability of PD patients appears to profit only insufficiently from the standard therapies used in the disease, such as L-dopa (Marsden, 1994). A worsening under L-dopa has even been reported in studies that assessed sway amplitude as a measure of postural instability (e.g. Bronte-Stewart *et al.*, 2002). On the other hand, improvements of motor functions under L-dopa therapy have been reported in studies that relied on clinical assessment scores such as the unified Parkinson's disease rating scale (UPDRS). For instance, the study by Bejjani *et al.* (2000) reports at least a partial improvement under L-dopa treatment for the 'axial signs' of the UPDRS, which are: arising from chair, posture, gait and postural stability, and for 'axial symptoms' in the supplementary scores from the 'activities of daily living', such as turning in bed, falling, freezing and walking, with most of the scores reaching statistical significance. Yet, there remains the fact that the effect of L-dopa treatment alone on postural instability becomes more and more unsatisfactory after several years of progression of the disease.

Over recent decades, surgical treatment of PD became a therapeutic option for patients in whom the effectiveness of medication was limited by motor response complications such as dyskinesias and strongly fluctuating motor states. A modulation of non-dopaminergic pathways by such interventions has repeatedly been proposed as a rationale for this approach. Originally, unilateral pallidotomy was used as an adjuvant treatment in advanced PD. Most studies of pallidotomy found major improvements in the majority of the motor subscores of the UPDRS, but hardly any long-term improvements of the scores related to posture control (see Bronte-Stewart *et al.*, 2002). The study by Bronte-Stewart *et al.*, however, reported a decrease in amplitude of spontaneous and externally evoked postural sway following pallidotomy, unlike under L-dopa medication.

High frequency chronic bilateral stimulation of the globus pallidum internus (GPI) or the subthalamic nucleus (STN) has become an alternative to pallidotomy in the treatment of PD patients. Both treatments have been shown to be clinically effective in ameliorating akinesia and rigidity and in reducing L-dopa-induced dyskinesias (Baron *et al.*, 1996; Krack *et al.*, 1998; Limousin *et al.*, 1998; Volkmann *et al.*, 1998; Jahanshahi *et al.*, 2000; Nutt *et al.*, 2001; Robertson *et al.*,

2001; Loher *et al.*, 2002). The study by Bejjani *et al.* (2000) reported a substantial improvement of most axial impairments in PD patients by STN stimulation and a synergistic treatment effect when the stimulation was combined with L-dopa treatment. Furthermore, a tremendous improvement of gait following STN stimulation has recently been demonstrated (Faist *et al.*, 2001).

However, the effect of such deep brain stimulations and of their combination with L-dopa treatment on patients' impaired posture control remains to be evaluated. A recent study by Rocchi *et al.* (2002) reported an improvement in the control of spontaneous sway during quiet stance in patients with deep brain stimulations. Interestingly, the stimulation partially reversed a L-dopa-induced increase in sway amplitude, which may suggest a differential and possibly complementary effect of the deep brain stimulations. However, such a conclusion would be premature, since the subject group in this study was heterogenous, comprising three patients with GPI stimulation and three patients with STN stimulation. Concerning STN stimulation, previous work indicated a synergism with L-dopa for the axial signs (Bejjani *et al.*, 2000). On the other hand, GPI stimulation has been found to differ from STN stimulation in that it immediately reduces L-dopa-induced dyskinesias, while STN stimulation produces only a delayed improvement of these dyskinesias (Krack *et al.*, 1998).

The present study was undertaken to compare the effects of STN stimulation with those induced by L-dopa treatment for different well-defined parameters of spontaneous body sway during unperturbed stance. Of particular interest to us were the treatment effects on sway amplitude and the question of whether this measure allows a valid characterization of the patients' instability and the treatment effects. Normal subjects can voluntarily allow for large sway amplitudes without losing balance, at least during unperturbed stance. Our findings provide evidence that there are additional abnormalities in the spontaneous sway of PD patients, which can possibly explain their postural instability better than the sway amplitude measure.

Furthermore, we assessed abnormalities of postural responses to external perturbations in the PD patients and the effect of STN stimulation and L-dopa treatment on these abnormalities. To this end, we presented our subjects with slow support surface tilt stimuli and measured their body excursions, differentiating between the excursions of the upper body (UB) and lower body (LB) segments (shoulder-on-hip versus hip-on-feet excursions in space, respectively). In addition, we presented our subjects with tilts of the visual scene while they were standing on either a stable support surface or a slightly moving surface. The latter experiment was motivated by the earlier observation of abnormally strong responses to translatory motion of the visual surroundings in PD patients (Bronstein *et al.*, 1990). This abnormality appears not to be related to an impaired sensory input *per se*, since this is not affected to a considerable degree

Table 1 *Clinical data of patients immediately prior to testing*

Patient no.	Gender	Age at symptom onset (years)	Duration of L-dopa therapy before implantation (years)	Age at stimulation implantation (years)	Time since stimulation implantation (months)	UPDRS motor score			
						OFF treatment	L-dopa treatment	Stimulation	L-dopa + STN stimulation
1	M	27	7	34.5	19	67	16	11	4
2	M	29	14.5	44.5	10	71	27	10	3
3	M	47	12	59	20	31	13	5	4
4	M	33	12	47.5	14	43	7	6	5
5	F	38.5	11.5	52	5	39	14	5	2
6	F	30	4.5	38.5	38	52	7	4	2
7	F	34	12	47	11	61	18	9	7
8	M	40	11	51	6	31	7	9	6
Mean		34.8	10.6	46.8	15.4	49.4	13.6	7.4	4.1
SD		6.7	3.2	7.7	10.6	15.8	6.9	2.7	1.8

See Faist *et al.* (2001) for clinical data prior to implantation.
M = male; F = female.

by the disease (Waterston *et al.*, 1993; Bronstein *et al.*, 1996; Pinter *et al.*, 1999; Schieppati *et al.*, 1999).

Material and methods
Patients
Eight PD patients (three women and five men) with a mean age of 48.1 years (range 36–60 years) were investigated. These patients were the same as in the study by Faist *et al.* (2001) and represent a group with rather young onset of the disease (mean 34.8 years) as compared with the average onset of PD (~57 years). All had been operated on at the Grenoble University Hospital and received chronic bilateral STN stimulation according to criteria reported by Limousin *et al.* (1998). All patients had a clear response to L-dopa. Detailed clinical data are given in Table 1 (see also Faist *et al.*, 2001). Motor disability was evaluated on the motor subscale of the UPDRS; it ranged from 28 to 66 in the OFF stage and from 4 to 12 in the ON stage (optimal score 0; worst score 108). The Hoehn and Yahr (1967) rating before surgery was 3–5 in the OFF period, and 2–3 in the ON period and after surgery with stimulation alone. The Schwab and England (1969) score for activities of daily living before implantation amounted to 20–70% in the OFF period and 80–100% in the ON period. Six of the eight patients still required L-dopa after implantation, in doses from 50 to 750 mg. Additional medication included amantadine in one, pergolide in two and bromocriptine in three patients. Additionally, 10 control subjects were investigated (age range 32–64 years, mean 47.5 years; three women and seven men).

The posture analyses and clinical assessments were performed in the posturography laboratory of the Department of Neurology and Clinical Neurophysiology of the Freiburg University Hospital. Four different treatment conditions were used: (i) OFF treatment; (ii) L-dopa; (iii) STN stimulation; and (iv) L-dopa plus STN stimulation. One experimental session took ~1 h for each of the four

conditions, interrupted by pauses for rest. Two conditions were performed per day in an early morning session and a late morning session, so that 2 days were required per patient. The night prior to each experiment, patients fasted and took no medication. In the early morning sessions of the following day we always tested either the OFF stimulation condition (after at least 30 min of stimulation arrest) or the ON stimulation condition. Then patients took their medication in the late morning and continued with either the L-dopa or the L-dopa plus STN stimulation condition (condition 4). Within this framework the order of conditions was randomized such that on the first day four patients always started with one condition in a session and the remaining four with the other condition. The assessments in the ON medication conditions always were performed 40 min after the administration of a supra-threshold dose of 200–300 mg liquid L-dopa and 50–75 mg benserazide (dispersible Madopar®) and a light breakfast as described in detail previously (Faist *et al.*, 2001). Thus, the experimental sessions on 1 day took 3–4 h, including ample time for rest.

Healthy control subjects performed the procedure only once. The study was approved by the ethics committee of the University of Freiburg, and all subjects gave their written informed consent.

Procedures
Spontaneous sway
The first experiment involved four measurements of spontaneous sway (80 s each) with subjects having their eyes open and closed, respectively. Stance width was always 7 cm. We recorded the 2D centre of pressure (COP) sway path with the help of a force transducing system (Kistler platform type 9286, Winterthur, Switzerland). Furthermore, we measured the position of the body segments using an optoelectronic device with active markers attached to the shoulder and to the hip (Optotrak 3020, Waterloo, Canada). Three markers were

placed at each level, fixed on a rigid triangle. A PC calculated on-line 3D translational and angular positions of each triangle, from which we obtained UB and LB excursions in space, respectively. From these data we extracted the SDs of the COP linear excursions and LB and UB angular and linear excursions in anterior–posterior (a-p) and in lateral directions (sagittal and frontal planes, respectively). After differentiating, we obtained from these data the corresponding velocity time series and calculated the mean magnitude of sway velocity in the a-p and lateral directions. In addition, we calculated from the COP excursions the root mean square distance (COP RMS) as a measure of the COP variability around the mean COP position and the line integral of the COP excursion (COP line integral).

To allow assessment of tremor-like oscillations, we calculated power spectral density (PSD) plots of these excursions and of the corresponding velocity time series (the low-frequency power of sway is better reflected in displacement time series and the high-frequency power more in the velocity time series). Having noted a peak in the velocity PSD plots of the patients OFF treatment in the 0.7–1.1 Hz frequency range (see Results), we calculated in addition the contribution of the power in this frequency range to the overall power in the 0.0125–1.1 Hz range (in the following referred to as PSD ratio) for comparison across treatment conditions.

Furthermore, we evaluated a measure of inter-segmental UB-LB stiffness. Following a method described by Accornero *et al.* (1997), we obtained a measure of the inter-segmental UB–LB coupling by calculating the 3D velocity vectors of both segments at each 10 ms. From the angle between the two vectors we generated a single differential angle α with $\cos(\alpha) = V_{LB}^2 + V_{UB}^2 - (V_{UB} - V_{LB})^2 / (2 \cdot |V_{UB}| \cdot |V_{LB}|)$, where V_{LB} represents the vector of the lower body and V_{UB} the vector of the upper body. Note that a differential angle of $\alpha = 0°$ corresponds to a situation where hip and shoulder move in fixed register in the same direction in space (both segments strictly coupled; maximal error by noise <1°). A differential angle of $\alpha = 90°$ would mean that hip and shoulder move completely independently of each other in orthogonal directions.

Platform tilt

The second experiment investigated the subjects' postural responses to transient tilts of a motion platform in the a-p direction (sagittal plane). The stimuli were applied in two series, one with subjects having the eyes closed and the other with the eyes open in front of a stationary 3D virtual reality scene (see Maurer *et al.*, 2000). Subjects' task was to 'always maintain upright body orientation in space'. The stimulus profile of the platform tilt followed a raised cosine velocity function [Maurer *et al.*, 1997; $v_{(t)} = - A \cdot f \cdot \cos(2\pi f \cdot t) + A \cdot f$, where f = 0.2 Hz, A = 4°]. The tilt axis was through the ankle joints. Four tilts toes-up and four tilts toes-down were presented in random order. LB and UB angular excursions

were measured as described above. Note that the LB angular excursions reported in the following closely resemble the excursions of the centre of body mass, since this is located only some centimetres above the hip, where we measured the LB excursions (ascertained by calculating the centre of body mass excursions according to Winter, 1995).

Visual tilt

The third experiment investigated, with the same instruction as before, subjects' postural responses to tilt of the visual scene, again in the sagittal plane (and with the visual tilt axis through the ankle joints). The 3D virtual reality scene was sinusoidally tilted at 0.1 Hz with different peak angular excursions (A = ±0.5°, ±1°, ±2° and ±4°). The stimulus presentation contained seven full cycles of the stimulus. Two support surface conditions were used in separate experimental sessions. In one session the platform was kept stationary ('stable platform condition'), in the other session it was slightly moved ('unstable platform condition'; sinusoidal tilts at 0.25 Hz in a direction orthogonal to the visual stimulus, i.e. in the frontal plane, A = ±0.25°). Again, LB and UB angular excursions were measured.

Data analysis

Optotrak® and Kistler® output signals as well as the stimulus signals were transferred on-line to a computer system (IBM compatible Pentium®) via an analogue–digital converter at a sampling rate of 100 Hz. The data were recorded with software programmed in LabView® (National Instruments, Austin, TX, USA) and analysed off-line with custom-made software programmed in MATLAB (The MathWorks Inc., Natick, MA, USA). Within-subject averages of visual and platform tilt responses were obtained for a fixed number of trial repetitions per experiment. Further analysis was performed using a spreadsheet program (Microsoft Excel) and statistics programs (StatView® and SuperAnova®, SAS Inc., Cary, NC, USA). Responses to the sinusoidal visual tilts (third experiment) were furthermore analysed using discrete Fourier transformation (dft) of the input time series [(Y, f) = dft(X, Fs, Fpts)]. The output Y was scaled so that a unit time domain sinusoid corresponds to a unit amplitude in the frequency domain (X = input time series; Fs = sampling frequency of time series, 100 points/s; Fpts = number of frequency points to calculate beginning with the fundamental; Y = Fourier coefficients, complex numbers; f = frequency, in Hz). From Fourier coefficients of stimulus and response time series we calculated amplitude and phase values of the responses with respect to the stimulus across all full cycles in the stimulus presentation (n = 7).

Statistical significance was tested by analysis of variance (ANOVA) unless otherwise stated. The difference between normal subjects and patients OFF treatment was assessed by means of a factorial ANOVA with subject group as the 'between' factor ('between subject groups' ANOVA).
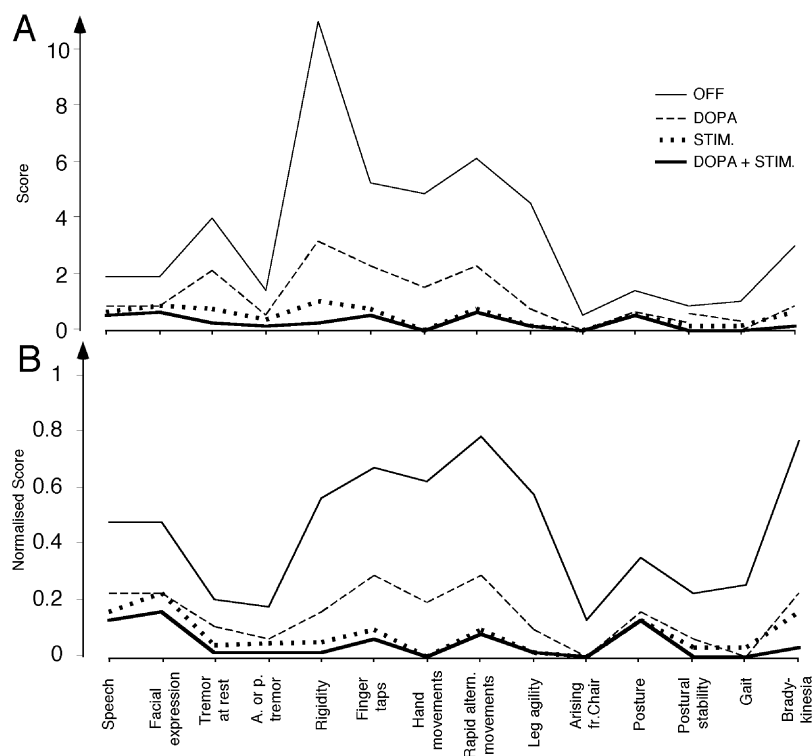
Fig. 1 Results of the motor subscores of the UPDRS as profiles that characterize the patients OFF treatment and their responses to the treatment regimes. Scores in absolute values (**A**) and in values normalized to the maximal possible impairment score (unity; **B**). The scores were always largest in the OFF treatment condition (OFF). They were significantly reduced with treatment. See text for details. DOPA = L-dopa treatment; STIM = STN stimulation; DOPA + STIM = L-dopa + STN stimulation.

Treatment effects in patients were analysed by means of another ANOVA with treatment condition as the within-subjects factor ('within patients' ANOVA). Differences between treatment conditions were tested with the non-parametric Wilcoxon signed-rank test. Correlations among spontaneous sway data and between these data and the results of the motor subscores of the UPDRS were evaluated with the non-parametric Spearman's rank correlation test. Bonferroni corrections and interactions were calculated for the repeated measures of the visual tilt responses to different stimulus amplitudes.

Results
Clinical data
Results from the UPDRS motor examination are presented in Table 1 for the four treatment conditions. L-dopa improved the sum of the motor exam scores significantly (reduced the clinical signs), as did the STN stimulation and, even more pronounced, the combination of both treatments. The results of the UPDRS subscores are represented in Fig. 1 as profiles that characterize our patients and their responses to the treatment regimes. The scores were always largest in the OFF treatment condition. They were significantly reduced ($P <$ 0.05) with L-dopa, STN stimulation and the combination of the two treatments. The only exception was the subscore tremor at rest (tremor was present in only two of the eight patients in the OFF treatment condition). Interestingly, a significantly greater improvement ON STN stimulation than ON L-dopa treatment was found for the subscores finger taps and rapid alternating movements. Furthermore, significantly greater improvements under combined treatment as compared with L-dopa alone were observed for the subscores rigidity, finger taps, hand movements, rapid alternating movements and bradykinesia.

Spontaneous sway
Representative examples of COP trajectories during unperturbed quiet stance with eyes open are given in Fig. 2 from a control subject (Fig. 2A) and two PD patients (Fig. 2B and C–F). Note that the sway areas of both patients are larger than that of the control subject. The data shown in Fig. 2C–F comprise the four treatment conditions. In the OFF treatment condition (Fig. 2C), the patient's COP shows a tremor, more in the lateral than in the a-p direction, in addition to the abnormally large sway area. Upon L-dopa treatment (Fig. 2D), this area became larger and the tremor disappeared almost completely. In addition, STN stimulation led to an increase in sway area and to a suppression of the tremor (Fig. 2E).
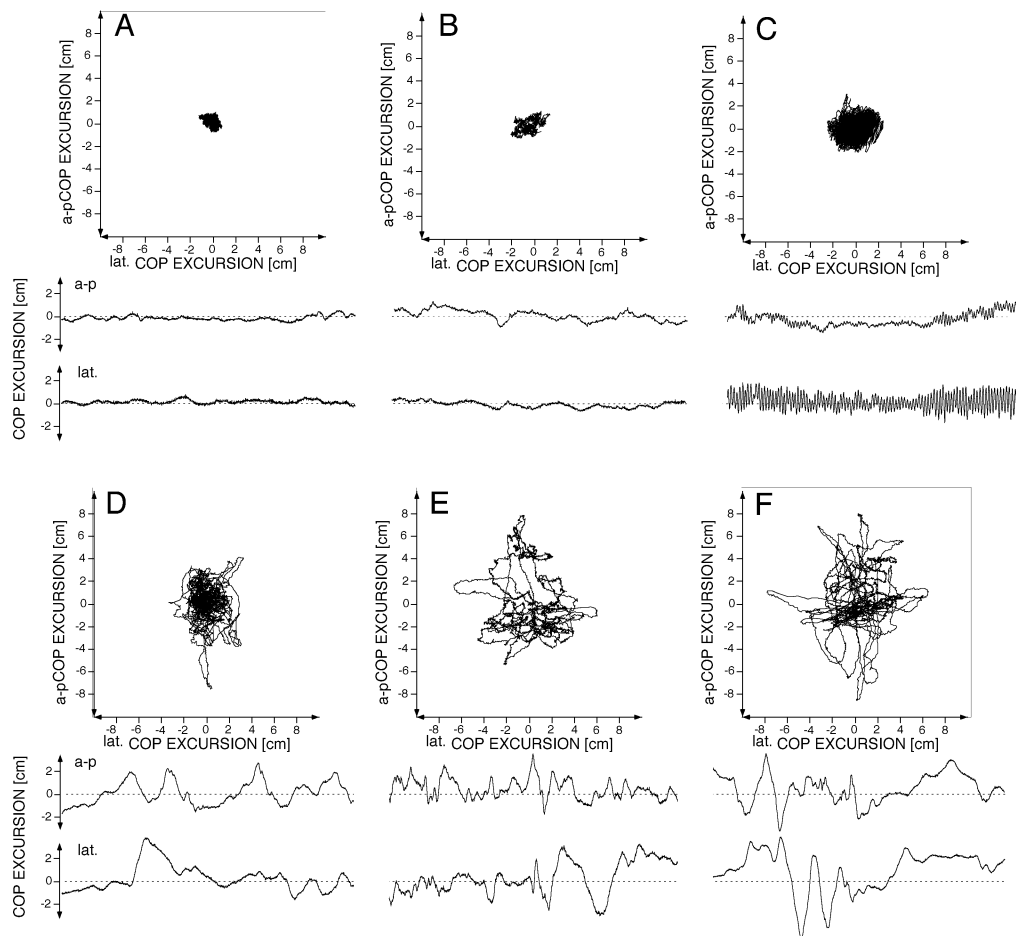
Fig. 2 Representative examples of COP trajectories during unperturbed quiet stance. (**A**) Control subject. (**B**) PD patient without tremor (OFF treatment). (**C–F**) PD patient with tremor in the (**C**) OFF treatment condition, (**D**) ON L-dopa treatment, (**E**) STN stimulation and (**F**) the combination of these two treatments. Upper panels: 2D COP displacement plots. Lower panels: 20 s cut-outs of the corresponding 80 s time series in anterior–posterior (a-p) and lateral (lat.) direction. Data are referenced to corresponding mean values.

Similar effects were observed when the two treatments were combined (Fig. 2F). Tremor of a similar magnitude as in Fig. 2C was observed in one more patient in the OFF treatment condition, whereas no tremor was seen in the data of the remaining six patients. Noticeably, there was no L-dopa- or STN stimulation-induced dyskinesia in all patients.

When comparing our quantitative measures of spontaneous sway between the eyes open versus the eyes closed conditions, we found no statistically significant differences, in either the control subject group or the patient group. We therefore pooled the data for the following descriptions of the inter-group differences and treatment effects.

Patients OFF treatment versus control subjects

COP displacement in terms of mean SD values (Fig. 3A) in the patients OFF treatment was larger by a factor of approximately two as compared with the control subjects.

This applied similarly in the a-p and lateral directions ($F_{\text{a-p}} = 53.6$, $P < 0.0001$; $F_1 = 28.6$, $P < 0.0001$). The SD values for angular excursions of the LB (Fig. 3B) and the UB (Fig. 3C) showed similar differences between the patients and the controls (LB: $F_{\text{a-p}} = 30.0$, $P < 0.0001$; $F_1 = 16.2$, $P < 0.0001$; UB: $F_{\text{a-p}} = 51.1$, $P < 0.0001$; $F_1 = 16.8$, $P < 0.0001$). In addition, the COP RMS (2D RMS of the distance of the COP from the centre of sway) and the COP line integral were larger in patients than in the controls by a factor of approximately two (not shown).

Mean magnitudes of COP velocity in the a-p direction and the lateral direction (Fig. 3D) were larger in the patients OFF treatment than in the controls ($F_{\text{a-p}} = 10.0$, $P = 0.002$; $F_1 = 16.0$, $P < 0.0001$). This also applied when the two patients with tremor were excluded from analysis (asterisk in Fig. 3D). There was an asymmetry in velocity, i.e. it was higher in the lateral direction than the a-p direction, both in the controls and the patients. In addition, mean magnitude of LB angular velocity (Fig. 3E) and UB angular velocity (Fig. 3F) were
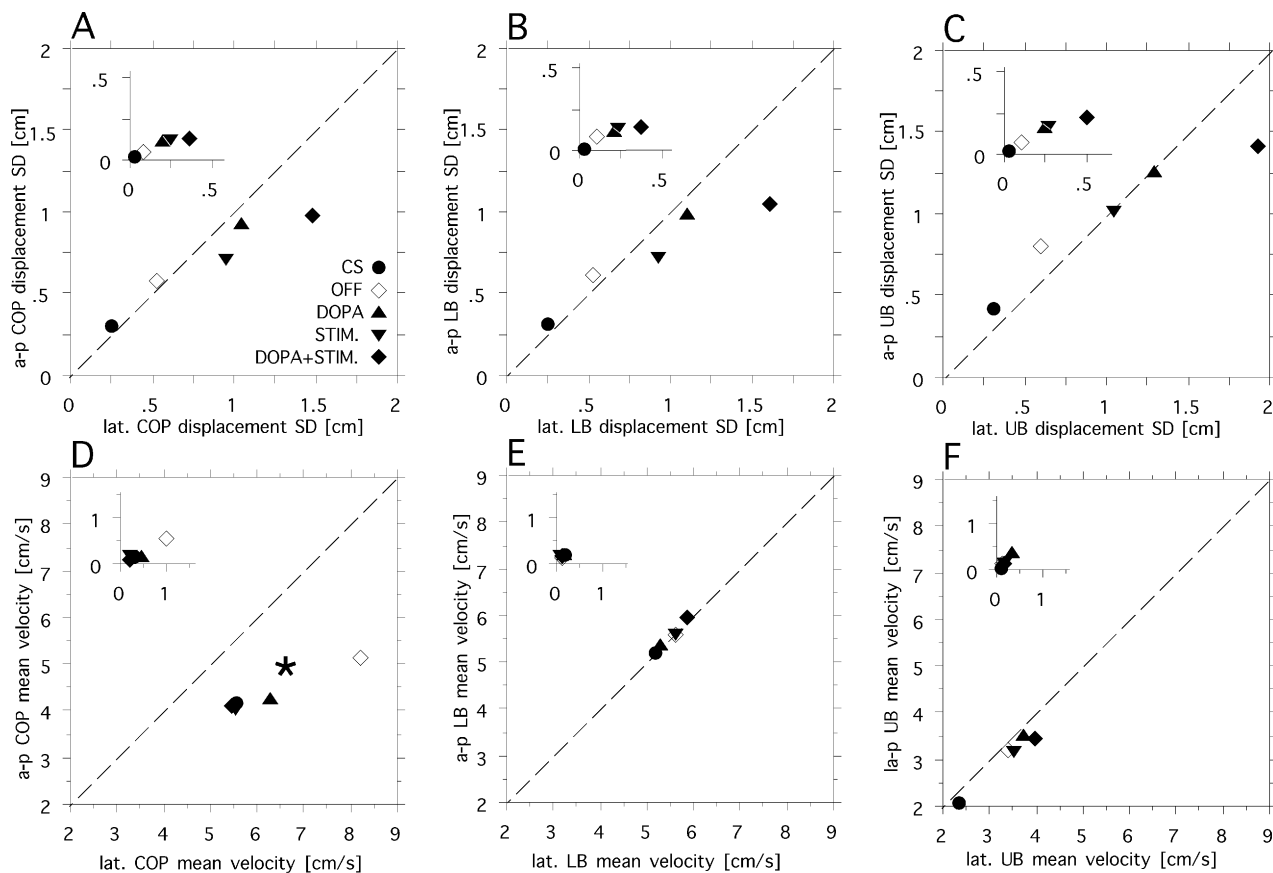
Fig. 3 Measures of spontaneous body sway in the PD patients for the four treatment conditions and in the control subjects (CS). (**A–C**) COP, LB and UB sway amplitudes in terms of averaged intra-individual displacement SD values in anterior–posterior (a-p) and lateral (lat.) directions. (**D–F**) The corresponding mean velocity values of COP, LB and UB. Note that the angular excursions of the LB and UB segments are given here as linear excursions for better comparison with the COP. Insets give the corresponding inter-individual SD values. Treatment conditions in patients: OFF = OFF treatment; DOPA = L-dopa treatment; STIM = STN stimulation; DOPA + STIM = L-dopa + STN stimulation. The asterisk in **D** gives the mean velocity values of the patients in the OFF treatment condition after excluding the two patients with tremor.

larger in the patients (LB: $F_{\text{a-p}} = 8.3$, $P = 0.004$; $F_l = 11.1$, $P = 0.001$; UB: $F_{\text{a-p}} = 104.6$, $P < 0.0001$; $F_l = 104.3$, $P < 0.0001$), but they did not show such a pronounced asymmetry as the COP velocity measure.

Figure 4A shows the mean PSD curves for the COP, LB and UB excursions in the lateral direction of both patients OFF treatment and normal controls with eyes open. The overall power is clearly larger in the patients than in the controls, both in the low frequency range (left panels; 0.01–0.1 Hz) and in the mid- and high-frequency ranges (right panels; 0.11–1 and 1.1–10 Hz, respectively). Furthermore, patients' PSD curves of COP velocity showed a pronounced peak at ~5 Hz. It was observed only in the two patients who showed tremor in the COP displacement time series and was not present in the other patients. There is, in addition, a peak in the 0.7–1.1 Hz range in patients, much more pronounced in the COP than in the LB and UB PSD velocity plots. Qualitatively very similar findings were obtained in the

corresponding curves for the a-p direction as well as for both directions in the eyes closed condition (not shown). Note that the peak in the 0.7–1.1 Hz range shows less power and is shifted towards lower frequencies when going from the COP to the LB and UB PSD velocity plots, which indicates that it originates from leg muscle activity and not from movements at the level of the hip or the shoulders (e.g. from abnormal limb movements).

Our measure of the inter-segmental UB–LB coupling (mean angle between the two 3D velocity vectors, denoted in Fig. 5B as 'uncoupling measure') amounted to 32° in the control subjects and 20° in the patients OFF treatment, on average (difference statistically significant; $F = 9.1$, $P = 0.002$). The smaller value in the patients indicates a tighter inter-segmental coupling, compatible with an abnormally high inter-segmental stiffness (mean values in a normal population of young and elderly subjects amounted to 39.6° and 28.8°, respectively; see Accornero *et al.*, 1997).
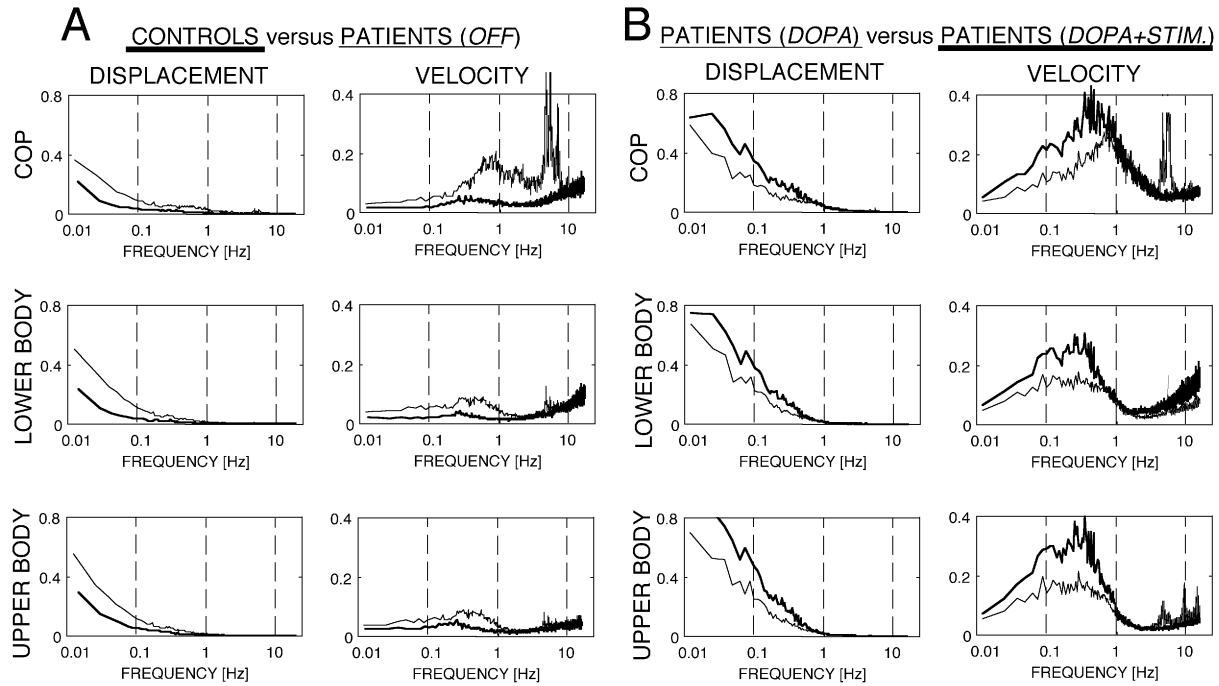
Fig. 4 Mean PSD plots from the displacement and velocity times series of the COP, LB and UB excursion in the lateral direction (eyes open condition). (**A**) Superposition of PSD curves of normal controls and the PD patients OFF treatment. (**B**) Superposition of PSD curves of the patients ON treatment with L-dopa and with the combination of L-dopa + STN stimulation. Note that the overall power in the patients' curves is always larger than in the controls. Furthermore, the patients' PSD curves of COP velocity in the OFF treatment condition show a pronounced tremor peak at ~5 Hz and, in addition, a peak between 0.7 and 1.1 Hz (presumed to reflect a resonance behaviour of the postural feedback control loop).
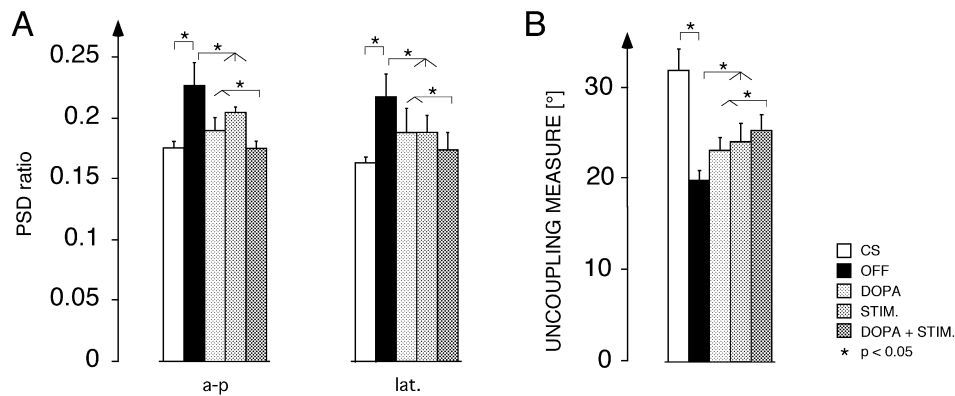

Fig. 5 (**A**) PSD ratios (ratios of the power in the 0.7–1.1 Hz frequency range to the overall power in the 0.0125–1.1 Hz range) of the corresponding COP velocity PSD plots in lateral direction (pooled data of eyes open and eyes closed conditions) of control subjects (CS) and the PD patients in the four treatment conditions. Note that the ratios of the patients OFF treatment were significantly larger than those of the controls and those ON treatment. Furthermore, the patients' ratios under the combination of L-dopa + STN stimulation were significantly smaller than those under L-dopa or STN stimulation alone. *$P < 0.05$. (**B**) Measure of the inter-segmental UB–LB coupling ('uncoupling measure', mean angle between UB and LB 3D vectors). The smaller values in the patients indicate a tighter inter-segmental coupling. *$P < 0.05$.

Effects of L-dopa and STN stimulation in patients
The abnormally large COP excursions (high displacement SD values) in patients OFF treatment were further increased by treatment, in both the a-p and lateral directions (Fig. 3A). This applied to L-dopa ($P_{a-p} < 0.0001$; $P_l = 0.003$), STN stimulation ($P_{a-p} = 0.03$; $P_l = 0.02$) and the combination of

both treatments ($P_{a-p} < 0.0001$; $P_l < 0.0001$). The effect of the combined treatment essentially reflected the sum of the individual treatment effects. Treatment increased the COP excursions more in the lateral than in the a-p direction, with the most pronounced asymmetry in the combined treatment condition. Very similar treatment effects were obtained for

the LB and UB displacement SD values (Fig. 3B and C). Note from the insets in Fig. 3A–C that these effects were associated with almost parallel increases in the inter-subject variability of the data. Analogous treatment effects were obtained for the COP RMS and the COP line integral. Both measures increased with L-dopa and with STN stimulation, and further increased when these treatments were combined (not shown).

Treatment decreased the abnormally high magnitude of COP velocity in patients as compared with the OFF treatment condition (Fig. 3D). This applied to L-dopa ($P_{a-p} = 0.0002$; $P_l < 0.0001$), STN stimulation ($P_{a-p} < 0.0001$; $P_l < 0.0001$) and the combination of the two ($P_{a-p} < 0.0001$; $P_l < 0.0001$). The effect of L-dopa was slightly weaker than that of STN stimulation, where the values essentially reached the range of the controls, and no further effect was obtained with the combination of the two treatments. Mean magnitude of LB and UB velocities were similarly affected by treatment.

Treatment was associated with pronounced changes in the PSD plots (Fig. 4B; lateral direction, eyes open condition). L-dopa treatment was associated with a pronounced increase in the power of the COP excursion in the low- and mid-frequency ranges as compared with the OFF treatment condition (compare Fig. 4A). Furthermore, the peak at ~5 Hz was reduced. Similar effects were observed with STN stimulation (not shown). Combination of the treatments further increased the power, eliminated the 5 Hz peak and led to a further shift of the power towards lower frequencies (Fig. 4B, upper velocity panel). Very similar treatment effects in the PSD plots were obtained for the LB and UB excursions (Fig. 4B, corresponding middle and lower panel). This also applied to the a-p direction and in the eyes closed condition (not shown).

The PSD ratios of the corresponding velocity time series are given in Fig. 5A (ratios of the power in the 0.7–1.1 Hz range to the overall power in the 0.0125–1.1 Hz range in the PSD plots after pooling the data of the eyes open and eyes closed conditions). The ratio showed a reduction under L-dopa treatment in both the a-p and lateral directions ($P_{a-p} = 0.009$; $P_l = 0.05$). A similar, but slightly weaker reduction was found for STN stimulation ($P_{a-p} = 0.04$; $P_l = 0.05$) and a stronger effect with the treatment combination ($P_{a-p} = 0.003$; $P_l = 0.04$). Under combined treatment, the ratios became similar to those of the control subjects ($P_{a-p} = 0.58$; $P_l = 0.17$).

Treatment also improved the abnormally tight UB–LB coupling of the patients (Fig. 5B). Compared with the OFF treatment condition, the uncoupling measure became larger with L-dopa ($P = 0.008$), STN stimulation ($P = 0.005$) and the combination of the two treatments ($P = 0.002$). There was a trend for a larger effect with the combined treatment as compared with L-dopa alone and stimulation alone ($P = 0.07$ and 0.08, respectively).

Correlations
Table 2A shows the results from the Spearman's rank correlations among the above described sway measures. Note that the displacement SD values, the COP RMS and the line integral of COP, as well as the inter-segmental coupling, are highly correlated with each other (and with the total power of the COP PSD in the 0.0125–1.1 Hz frequency range; not shown). However, these measures did not correlate with mean magnitude of COP velocity and the PSD ratio. On the other hand, the latter two measures were highly correlated with each other, and correlated with the clinical data, as shown in Table 2B. This table gives the correlations between these COP data and the improvements under therapy in the motor subscores of the UPDRS. Note that the displacement SD, COP RMS and COP line integral measures were correlated solely with the item rapid alternating movements. The measure of inter-segmental coupling showed, in addition, correlation with arising from chair, gait and body brady-kinesia. In contrast, the magnitude of COP velocity and the PSD ratios correlated well with the improvements of the total UPDRS and with most of the subscores. Exceptions were speech, facial expression, posture, postural stability and gait (see Discussion).

Platform tilt
Patients OFF treatment versus control subjects
With the eyes closed, four of the eight patients had difficulties maintaining balance in the OFF treatment condition during the 4° forward (toes down) and/or the 4° backward (toes up) platform tilt, unlike the control subjects. We therefore restricted the experiment for all subjects to the platform tilts with the eyes open.

The responses of the control subjects to the 4° forward tilt are shown in Fig. 6 in terms of averaged UB excursion (Fig. 6A) and LB excursion (Fig. 6B) over time (±SD, hatched areas). The controls under-compensated the platform tilt, allowing a peak LB excursion in space of 1.9° ± 0.7° during the dynamic tilt phase, with some correction towards primary position during the following static phase (minimum excursion 1.3° ± 0.6°). Their UB excursions were clearly smaller (peak 0.2° ± 0.6°; minimum 0.1° ± 0.4). As illustrated in Fig. 6A ('stick figure' CS), there resulted an UB righting on the LB in the normal controls.

Patients OFF treatment showed somewhat smaller LB excursions in space than the controls during both the dynamic tilt phase (peak 1.2° ± 0.6°) and the static phase (minimum 0.7° ± 0.8°). However, their UB excursion was larger than their LB excursion; it amounted to 1.4° ± 1.2° for the peak and to 0.9° ± 0.7° for the minimum. Furthermore, their peak UB excursion was larger than that of the controls ($F = 6.7$; $P = 0.008$). The difference of the peak LB excursions between the two subject groups showed only a trend ($F = 2.6$; $P = 0.07$) and the corresponding differences for the minima also were statistically not significant. A similar response, but with clearly smaller amplitudes, was obtained with the 4° backward platform tilt, and the differences between the two subjects groups were here again statistically not significant.

Table 2A *Spearman's rank correlations among the sway measures of COP and intersegmental coupling*

	COP disp. SD a-p	COP disp. SD lat	Line integral	RMS	Intersegmental coupling	Magn. COP vel. a-p	Magn. COP vel. lat	PSD ratio a-p	PSD ratio lat.
COP disp. SD. a-p									
COP disp. SD lat.	0.0001								
Line integral	0.0001	0.0001							
RMS	0.0001	0.0001	0.0001						
Intersegm. coupling	0.0004	0.0002	0.0005	0.0002					
Magn. COP vel. a-p	n.s.	n.s.	n.s.	n.s.	n.s.				
Magn. COP vel. lat.	n.s.	n.s.	n.s.	n.s.	n.s.	0.0001			
PSD ratio a-p	n.s.	n.s.	n.s.	n.s.	n.s.	0.0001	0.0001		
PSD ratio lat.	n.s.	n.s.	n.s.	n.s.	n.s.	0.02	0.0003	0.0001	

Table 2B *Spearman's rank correlations among the sway measures of COP and the UPDRS and its subscores*

	COP disp. SD a-p	COP disp. SD lat	Line integral	RMS	Intersegm. coupling	Magn. COP vel. a-p	Magn. COP vel. lat	PSD ratio a-p	PSD ratio lat.
UPDRS motor sum	n.s.	n.s.	n.s.	n.s.	n.s.	0.003	0.0001	0.002	0.0006
Speech	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Facial expressions	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Tremor at rest	n.s.	n.s.	n.s.	n.s.	n.s.	0.0003	0.0001	0.0006	0.0008
Anterior or posterior tremor	n.s.	n.s.	n.s.	n.s.	n.s.	0.0001	0.0001	0.0005	0.0003
Rigidity	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0.0008	0.04	0.002
Finger taps	n.s.	n.s.	n.s.	n.s.	n.s.	0.01	0.0001	0.01	0.005
Hand movement	n.s.	n.s.	n.s.	n.s.	n.s.	0.02	0.002	0.002	0.006
Rapid alternating movements	0.05	0.04	0.05	0.04	0.03	n.s.	0.006	0.001	0.01
Leg agility	n.s.	n.s.	n.s.	n.s.	n.s.	0.004	0.0001	0.001	0.01
Arising from chair	n.s.	n.s.	n.s.	n.s.	0.04	0.008	0.005	0.002	0.02
Posture	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Gait	n.s.	n.s.	n.s.	n.s.	0.02	n.s.	n.s.	n.s.	n.s.
Postural stability	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Body bradykinesia	n.s.	n.s.	n.s.	n.s.	0.04	0.05	0.0006	0.006	0.002

lat. = lateral; vel. = velocity; magn. = magnitude; a-p = anterior–posterior; disp. = displacement; n.s. = not significant.

Effects of L-dopa and STN stimulation in patients
The platform tilt responses of the patients under STN stimulation and the combined treatment are superimposed on the previous data in Fig. 6. The results obtained for L-dopa treatment were very similar and are illustrated in Fig. 6B ('stick figure' DOPA). Patients' responses in the three treatment conditions did not differ from each other, nor did these responses differ from those in the OFF treatment condition. Accordingly, patients' responses to support surface tilt did not correlate with the improvements of the UPDRS or its motor subscores under treatment.

Visual tilt
Patients OFF treatment versus control subjects
Figure 7A shows the peak UB and LB excursions of the control subjects evoked by the sinusoidal a-p rotations of the visual scene at 0.1 Hz. The results of the stable platform condition are superimposed on those of the unstable platform condition ($\pm 0.25°$ sinusoidal platform rotation at 0.25 Hz in lateral direction, i.e. the frontal plane). A representative

example of the LB excursions of a control subject in the stable platform condition is inserted in Fig. 7A. The responses are relatively small in comparison with spontaneous sway, indicating that the subject was largely suppressing body lean in response to the visual tilt. This applied similarly to all stimulus amplitudes tested (see the response curve of the mean $\pm$ SD values). Responses of similar magnitude were obtained for the UB (compare also 'stick figure' CONTROLS). In contrast, in the unstable platform condition both the LB and UB responses increased with increasing stimulus amplitude up to $\pm 2°$ tilt, after which they saturated with the $\pm 4°$ stimulus. The difference between the two platform conditions was statistically significant (UB: $F = 8.7$, $P = 0.003$; LB: $F = 8.4$, $P = 0.004$; interaction with stimulus amplitude was not significant in these and the following comparisons). Taking the two experiments together, stability of the support surface helped the control subjects to suppress body lean in response to visual tilt.

In the stable platform condition, the response amplitudes of the patients in the OFF treatment condition (Fig. 7B) were larger than those of the controls (UB: $F = 19.0$, $P = 0.0001$; LB: $F = 14.8$, $P = 0.0003$). A representative example of the
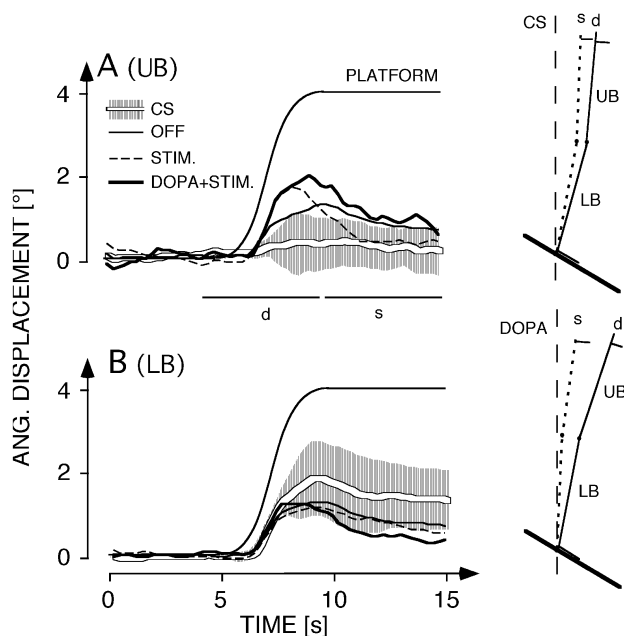
Fig. 6 Results of the platform tilt experiment. Averaged responses to transient toes-down (forward) platform tilt (4°) in the presence of a stationary visual scene. The response curves give the angular displacements of (**A**) the UB and (**B**) the LB in space over time. The hatched areas represent the controls (mean ± SD). Patients' responses for the treatment conditions OFF, STIM and DOPA + STIM are superimposed. *Right*: stick figures representing peak UB and LB excursions of the control subjects (CS) and of the patients treated with L-dopa (DOPA) during the dynamic tilt phase (d) and the corresponding excursion minima during the following static phase (s) (magnification factor of lean = 8). These insets illustrate that an UB righting on the LB, present in the control subjects, is missing in the patients.

LB excursions from one of the patients is inserted in Fig. 7B for the stable platform condition. In the unstable platform condition, patients' responses were similar to those of the controls (UB: $F = 1.2$, $P = 0.3$; LB: $F = 2.5$, $P = 0.1$). Notably, patients' responses were essentially independent of the platform condition (UB: $F = 0.3$, $P = 0.6$; LB: $F = 1.1$, $P = 0.3$), indicating that stability of the support surface did not help the patients to suppress body lean in response to visual tilt. The phase values of the UB and LB responses essentially equalled each other and both values were similar in patients and controls, independent of stimulus amplitude and platform condition (grand averages: phase lead of ~23° in patients and ~25° in controls).

Effects of L-dopa and STN stimulation in patients

Patients' LB responses ON treatment were not significantly different from those in the OFF treatment condition (platform stable, $F = 2.5$, $P = 0.08$; platform unstable, $F = 2.6$, $P = 0.06$). Response variabilities were also similar. Their UB excursions, in contrast, showed a statistically significant increase

ON treatment (platform stable, $F = 3.3$, $P = 0.02$; platform unstable, $F = 3.9$, $P = 0.01$). In addition, variability of these responses increased. The increase of the UB responses was independent of the platform condition ($F = 0.07$, $P = 0.97$). The increase obtained with L-dopa treatment (Fig. 7C) was similar to that with STN stimulation (Fig. 7D; differences from the OFF treatment condition, $P = 0.03$ and 0.04, respectively; difference between these two treatment conditions, $P = 0.68$). The increase also applied to the combined treatment (Fig. 7E; $P = 0.03$), where it became largest (see 'stick figure' inset for patients). The phase values of the UB and LB responses remained essentially unchanged under treatment.

Discussion

In this study we found that patients with PD show pronounced abnormalities of their control of unperturbed upright stance, i.e. of their spontaneous sway. The sway parameters we measured in the presence of a visual reference (eyes open; virtual reality scene) were not statistically different from those obtained with the eyes closed in the patients and controls. It is true that previous studies observed considerable differences in spontaneous sway between these two conditions (e.g. Day *et al.*, 1993), but the effect appears to depend critically on the characteristics of the visual scene (Paulus *et al.*, 1994) and possibly also on individual idiosyncrasies (Lacour *et al.*, 1997).

Furthermore, we found that some, but not all, measured parameters of postural control during unperturbed stance changed under L-dopa therapy. STN stimulation then showed similar effects to L-dopa, and a combination of the two therapies yielded synergistic effects. In addition, patients' responses to external perturbations are impaired, but L-dopa and STN stimulation, alone or in combination, hardly affected these deficits.

Postural abnormalities in PD patients during unperturbed stance and effects of treatment

Spontaneous COP excursions of PD patients OFF treatment were abnormal in that they were enlarged and their mean velocity was increased. The sway contained abnormally high frequencies, even when the two patients with postural tremor were excluded from analysis. Very similar results were reported in a recent study by Rocchi *et al.* (2002).

We found furthermore an abnormally high inter-segmental UB–LB coupling in the patients OFF treatment. We relate this finding to an abnormally high inter-segmental stiffness of the patients, in line with the axial rigidity as a cardinal symptom of the disease. An increased stiffness, associated with more co-contraction and a larger background EMG activity, has been reported previously for ankle joints in PD patients (Dietz *et al.*, 1993; Burleigh *et al.*, 1995). To what extent can such an increase in ankle stiffness explain the
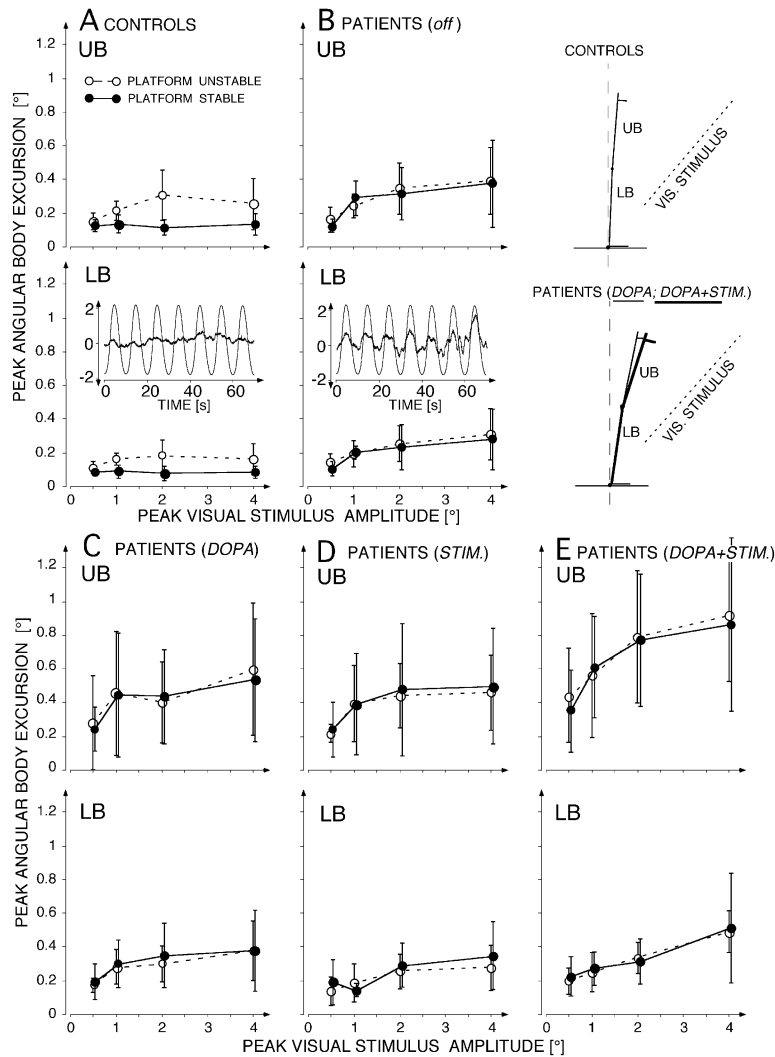
Fig. 7 Results of the visual tilt experiments. The responses to the sinusoidal stimulus (frequency = 0.1 Hz) in the sagittal plane are given as mean values of peak angular excursion (±SD) of the UB (upper panels) and the LB (lower panels) in space as a function of peak stimulus amplitude. (**A**) Normal controls. (**B–E**) Patients under the four different treatment regimes as indicated. Full inter-connecting lines denote responses to stable platform condition; the corresponding dashed curves denote unstable platform condition. **A** and **B** contain examples of LB excursions from a control subject and from a patient OFF treatment, respectively (stimulus amplitude ±2°). *Right*: stick figures representing mean peak UB and LB excursions of the control subjects and of the patients treated with L-dopa and with the combination of L-dopa + STN stimulation (always stable platform condition; visual tilt ±2°; magnification factor of lean = 20). Note in **B–F** that the patients' responses are very similar in the two platform conditions, while those of the controls (**A**) are smaller in the stable platform condition than in the unstable platform condition.

large, fast and high frequency sway of the patients OFF treatment? A passive system with high stiffness tends, indeed, to sway faster and at higher frequencies than one with low stiffness. However, this system would show a reduced rather than an enlarged sway amplitude, which makes such a simple mechanical explanation unlikely. Furthermore, a high stiffness of a passive system would tend to take a subject's body along with the support surface during platform tilt and would yield a large body excursion, contrary to our findings (see below).

These apparent discrepancies can be resolved if one takes into account that postural control represents primarily a sensorimotor feedback system and that rigidity in patients OFF treatment is actively produced. Rigidity in PD patients is primarily not related to changes in muscle properties; previous work failed to detect abnormal parameters of muscle contraction in lower leg muscles of patients with PD (Hufschmidt *et al.*, 1991). Instead, it appears to be of central origin, since deep brain stimulation, similar to L-dopa, is able to reduce it within minutes (as was the case in our study, for

instance). Rigidity in the patients is associated with an abnormally large magnitude and long duration of the long-latency stretch reflex in leg muscles (Tatton and Lee 1975; Berardelli *et al*., 1983; Rothwell *et al*., 1983). It is therefore thought to arise from supraspinal mechanisms, unlike spasticity, which is believed to be due to hyperexcitability of spinal stretch reflexes. While spasticity shows mainly a velocity-dependent increase in muscle tone upon stretch (analogous to a viscous resistance), rigidity is present even during very slow velocity stretch (elastic resistance), but in addition contains a velocity-dependent component (Lee *et al*., 2002). In sensorimotor control models, the active elastic property is generally implemented in the form of a proportional controller and the viscous one as a derivative controller. A proportional/derivative controller is required to adequately control the movements of a body segment with its inertia. Note that the term stiffness is used here in a general sense, whereas its use in control theory is restricted to the effect of the proportional controller.

It has recently been shown for a multisensory feedback control model of human upright stance (Peterka, 2002) that a below-normal gain of the proportional/derivative controller may lead to a resonance behaviour of the system at low frequencies (slow and abnormally large sway) and that an above-normal gain results in a resonance in the 0.7–1.0 Hz frequency range (fast and abnormally large sway). A resonance behaviour can also be found when the ratio of the proportional and derivative controller gains is changed or when the delay time of the system is increased, with noise in the system producing 'spontaneous' body sway (as we have ascertained by simulations of our own human postural control model; Mergner *et al*., 2003; see also Peterka, 2000). The peak in the 0.7–1.1 Hz frequency range that we observed in the PSD plots of PD patients OFF treatment may therefore reflect a resonance behaviour of the sensorimotor control loop and explain the abnormally large and fast sway (also see below). This notion is still speculative, but it may well serve as a working hypothesis for further considerations and future studies.

Others (Rocchi *et al*., 2002) have attributed the abnormally large sway of the patients mainly to deficits in fine tuning movements that may be related to poor use of somatosensory information. Indeed, there are studies that suggest an inappropriate use of kinaesthetic and proprioceptive information in patients with PD (Klockgether *et al*., 1995; Jobst *et al*., 1997; Rickards and Cody, 1997; Khudados *et al*., 1999). A reduced or inappropriate effectiveness of the sensory processing in the postural control loop may therefore have contributed to the abnormally large sway at low frequencies. Conceivably, the deficit might not necessarily be a pure sensorimotor one; given that spontaneous sway might involve a predictive component (Loram and Lakie, 2002), it could well be related to an internally generated signal. The presumed deficit appears to be largely masked in patients OFF treatment by their abnormally large axial stiffness, as indicated by the further increase of sway amplitude in relation to the stiffness reduction ON treatment (see the significant correlation between the stiffness and the COP displacement measures in Table 2A). In this view, treatment-induced reduction of stiffness reveals a deficit in the patients' use of sensory or internally generated signals for posture control, and this deficit is not ameliorated by L-dopa therapy.

The stiffness and the COP displacement measures were not correlated with mean magnitude of COP velocity and the PSD ratio, which in turn were significantly correlated with each other (Table 2A). We therefore assume that the presumed resonance peak in the 0.7–1.1 Hz frequency range in patients OFF treatment is not the direct consequence of the stiffness (or an abnormal increase in proportional/derivative controller gain producing the stiffness), nor is the shift of this peak towards lower frequencies under treatment the direct result of the stiffness reduction. The peak might, instead, result mainly from a mismatch between the proportional and derivative gains and/or an abnormally long time delay of the system (e.g. a time delay prolongation of 30 ms produces a dramatic effect; see Peterka, 2000).

Thus, we assume two largely independent abnormalities in patients' postural control of unperturbed stance: an L-dopa resistant ineffectiveness of the control, revealed under stiffness reduction by L-dopa, and a 0.7–1.1 Hz resonance that is improved by L-dopa (the same holds for STN stimulation). This notion is supported by the finding that the COP velocity and PSD ratio measures differed in their behavioural consequences from the stiffness and the COP displacement measures, in that the former were highly correlated with the treatment-related improvements of the total UPDRS and its motor subscores, unlike the latter (Table 2B; see also below).

A so far puzzling finding is the asymmetry in COP velocity between the lateral direction and the a-p direction (Fig. 3D). It was present in the normal subjects and, more pronounced, in the patients OFF treatment. ON treatment, the velocity asymmetry of the patients was changed towards normal values, but an asymmetry in favour of the lateral direction emerged in the COP displacement (Fig. 3A). Similar findings have been reported previously (see Rocchi *et al*., 2002). It is possible that they are related to the mechanical coupling between hip and ankle joints; as pointed out by Day *et al*. (1993) this coupling differs markedly for sway in the lateral versus the a-p direction, with implications for the afferent control of the sway.

Externally perturbed stance
Tilt of the support surface

Our patients had difficulties in coping with the support surface tilt when this was presented with their eyes closed. We therefore restricted the experiment to tilt responses with the eyes open in the presence of a stationary visual scene. In this condition, and due to the fact that the stimulus was

relatively slow (dominant frequency 0.2 Hz), we assume that the sensory signals that governed subjects' tilt responses mainly stem from vestibular and visual inputs, which combine here in a synergistic way. Patients' responses in terms of LB excursions in the dynamic and static tilt phases were slightly smaller than those of the controls, independent of the treatment condition. We deem it likely that the patients, experiencing subjectively an instability when standing on the motion platform, tended to keep their body excursions small during the tilt, similar to the way that normal subjects do when repeatedly instructed to keep their bodies upright during the tilt as perfectly as possible. An abnormal UB response (see below) may have contributed to patients' attempt to prevent large LB responses during the tilt. We therefore assume that patients' responses to the synergistic vestibular and visual inputs are essentially normal, but we cannot make statements concerning a tilt response with vestibular input alone. However, there is a previous report of essentially normal responses to galvanic vestibular stimulation in mildly or moderately affected PD patients (Pastor *et al.*, 1993). Comparison with other studies that used rapid rather than slow support tilt or translation as stimuli (Rothwell *et al.*, 1983; Diener *et al.*, 1987; Scholz *et al.*, 1987; Schieppati and Nardone, 1991; Bloem *et al.*, 1992; Beckley *et al.*, 1993; Paquet and Hui-Chan, 1997) is difficult because the responses then are governed to a large degree by non-vestibular cues (somato-sensory and proprioceptive).

How can we explain that both the abnormally high axial stiffness of patients OFF treatment and the reduction of the stiffness ON therapy did not shape their LB tilt responses to any considerable degree? We assume that axial muscle stiffness is modulated in the vestibular feedback control system in a servo-like way (see set point principle in Mergner and Rosemeier, 1998). In this view, the supra-spinal drive signals for the agonist and antagonist muscles are modulated during the response by the sensory-derived postural command signal in a reciprocal way. This mechanism would make the postural responses largely independent of current co-contraction and thus actively produced stiffness. The concept can also be applied to voluntary movements and explains why these movements are largely independent of rigidity; at least, there is currently no evidence that rigidity is a relevant factor for bradykinesia in PD patients (Berardelli *et al.*, 2001).

Patients' responses to the support tilt contained, in addition, an abnormal UB excursion, again independent of the treatment condition. While the control subjects showed an UB righting (on the LB as platform), the patients showed the contrary, i.e. an UB excursion that was larger than the LB excursion. We interpret this finding in terms of a missing hip synergy in the patients' postural response to support tilt, in line with previous work (Horak *et al.*, 1992). Earlier observations of abnormal axial movements when getting up from a chair or turning in bed in PD patients by Marsden *et al.* (1982) were interpreted in a similar way. Such

difficulties can remain even when L-dopa therapy has improved limb rigidity and bradykinesia (Lakke, 1985; Roberts-Warrior *et al.*, 2000). Similar difficulties are found with structural lesions of basal ganglia and thalamus and appear to result from a disruption of pallidal projections to the supplementary motor area through the thalamus (Masdeu and Gorelick, 1988; Labadie *et al.*, 1989). The missing hip synergy in our patients was resistant to L-dopa treatment and STN stimulation.

Visual tilt

Our patients' postural responses to tilt of the visual scene on stationary support surface were abnormally large, in line with previous reports in the literature (see Introduction). Generally, the visual tilt response represents a compromise between the subject's tendency to orient the body with respect to the scene as a reference, on one hand, and a secondary vestibular response that limits the body excursion off the gravitational vertical, on the other hand (Peterka, 2002). In this view, our findings suggest that in this visual–vestibular interaction the visual response prevails over the vestibular one in PD patients. However, our findings with the visual tilt stimulus require that this view is qualified by a closer inspection of two additional findings.

One additional finding was that the patients cannot make use of information on support stability for suppressing the destabilizing body lean during visual tilt as normal subjects do. Previous psychophysical work on visual–vestibular interaction in normal subjects (Mergner *et al.*, 2000) showed that the visual contribution to human self-motion perception dominates when the visual scene is stationary, but becomes suppressed when the scene is moving. The underlying sensor fusion mechanism involves cognition. The visual–vestibular interaction in postural control may be based on a similar mechanism. Given this, one would assume that patients with PD have a problem in using cognitive mechanisms for their postural response, although their perception of such experi-mental situations appears to be intact (Waterston *et al.*, 1993; Bronstein *et al.*, 1996; Schieppati *et al.*, 1999). Evidence for this notion comes from earlier observations which indicate that patients have difficulties in changing their muscle activation pattern when the body support conditions are changed (Rogers *et al.*, 1987; Scholz *et al.*, 1987; Dietz *et al.*, 1988; Schieppati and Nardone, 1991; Horak *et al.*, 1992), or in switching between motor programs (Marsden, 1982), or in optimally adjusting the weighting of the sensory loops to environmental changes (Marsden and Obeso, 1994). Noticeably, L-dopa therapy did not improve this deficit in our patients to a considerable degree.

The second additional finding concerns the UB lean during the visual tilt. This was larger than the LB lean in both the normal controls and in the patients. This finding can possibly be explained by assuming that there exists in human postural control a visual orientation response (related to the visuo-motor working space for the hands and the eyes) which

affects the UB more than the LB and is superimposed on the LB stabilization response. Whereas treatment in the patients affected their LB response only slightly, it clearly increased the magnitude and the variability of their UB responses. We deem it likely that this increase represents, at least in part, a passive effect in the sense that axial stiffness reduction under treatment allowed the gravitational pull on the leaning UB to become more effective.

Effects of STN stimulation versus L-*dopa treatment*

A number of recent studies reported an improvement of akinesia and rigidity in PD patients upon L-dopa and STN stimulation as well as upon combination of these two treatments (Krack *et al.*, 1998; Jahanshahi *et al.*, 2000; Nutt *et al.*, 2001; Robertson *et al.*, 2001). In fact, chronic bilateral STN stimulation allows great reduction or even discontinuation of L-dopa treatment in the patients (Fraix *et al.*, 2000; Molinuevo *et al.*, 2000; Lopiano *et al.*, 2001; Moro *et al.*, 2002). In particular the motor subscores of the UPDRS for akinesia, rigidity and tremor, and gait improve with STN stimulation similar to, or even better than, with L-dopa (Kumar *et al.*, 1998; Limousin *et al.*, 1998; Bejjani *et al.*, 2000). Furthermore, synergistic treatment effects of L-dopa and STN stimulation on spatial gait measures, such as walking velocity, were observed in a previous study in which the same patients as in the present study were investigated (Faist *et al.*, 2001).

The present findings are in line with these previous observations in that the changes in the patients' spontaneous sway parameters observed with STN stimulation were essentially parallel to those observed under L-dopa treatment, and in that the combination of these treatments led to a synergistic summation of effects. The two treatments paralleled each other also with respect to the observed treatment failures. For instance, neither of them nor their combination improved patients' ability to profit from a stationary body support during visual tilt, or improved their deficit in UB righting during platform tilt.

In a recent study, Rocchi *et al.* (2002) investigated the effect of deep brain stimulation on postural control during unperturbed stance of a cohort of three patients with GPI electrodes and three patients with STN electrodes. These authors reported close-to-normal values under stimulation for sway area, mean sway velocity and a measure of sway frequency, on average. Furthermore, improved but not quite normal values were observed when combining the stimulation with L-dopa treatment, a finding that suggested a linear summation of the treatment effects in that the stimulation partially made up for the increased sway under L-dopa treatment. The authors considered that these results might stem mainly from the three patients with GPI electrodes. In fact, previous work has shown that STN stimulation and not GPI stimulation affects the motor scores of the UPDRS in a similar way to L-dopa (Krack *et al.*, 1998). In that study, only in acute testing did L-dopa-induced dyskinesia profit more from GPI than from STN stimulation, whereas in the long term the reduction of L-dopa, which was achieved by the stimulation, reduced dyskinesia also in the patients with STN stimulation (as was the case in our patients). Other factors might also contribute to the apparent discrepancies between the present results and those of Rocchi *et al.* (2002), such as differences in surgical procedure, electrodes localization in the STN, etc., and the time that elapsed between implantation surgery and the functional testing (15.4 months in our patients as compared with 6 months in the study by Rocchi *et al.*, 2002).

On retrospective request, our patients reported that they experienced a better postural stability in the three L-dopa and stimulation treatment conditions than in the OFF treatment condition, despite the rather large spontaneous sway under treatments (Fig. 2D–F). This is in line with an improvement of the item falling of the scores for 'activities of daily living' of the UPDRS under these treatment regimes in the study by Bejjani *et al.* (2000). How can we relate the subjectively improved postural stability to the objective findings in our study? We conceive that postural stability is only loosely related to sway amplitude, which can vary considerably already in normal subjects depending on the instruction. In fact, our measures of sway amplitude increased rather than decreased under therapy (in relation to stiffness reduction) and did not correlate with the improvements in the UPDRS (Table 2B), as mentioned before. Instead, we deem it likely that postural stability in PD patients is more critically related to their abnormally high sway velocity and frequency (i.e. to the presumed resonance behaviour of the control loop), which tended to become normal ON therapy. These treatment effects correlated well with the UPDRS (Table 2). Major exceptions among the correlations with the motor subscores of the UPDRS, such as stooped or flexed posture, can possibly be explained by the fact that the corresponding baseline values in the OFF treatment condition were already very low in our patients. As concerns gait, for instance, our patients revealed a pronounced improvement upon neurophysiological testing (Faist *et al.*, 2001). Furthermore, postural stability (retropulsion test) is estimated as a response to an external perturbation. Such responses appear not to profit from L-dopa and STN stimulation, as indicated by our patients' responses to visual and platform tilt. Overall, adverse effects of STN stimulation as compared with L-dopa were not observed in our study.

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