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RESEARCH ARTICLE

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Impact of subthalamic nucleus stimulation on the initiation of gait in Parkinson's disease

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Abstract The effects of subthalamic nucleus (STN) stimulation on the anticipatory postural actions associated with the initiation of gait were studied in ten patients with idiopathic Parkinson's disease undergoing therapeutic deep brain stimulation. Kinematic, dynamic and electromyographic analysis was performed before and while subjects were starting gait in response to an external cue. Effects of STN stimulation on the standing posture preceding the go signal included significant improvement of the vertical alignment of the trunk and shank, decrease of the hip joint moment, backward shift of the center of pressure (CoP) and reduction of abnormal tonic and/or rhythmic activity in the thigh and leg muscles. Responses to bilateral STN stimulation were more consistent than those evoked by unilateral stimulation. Moreover, comparison between postural changes induced by STN stimulation applied prior to the gait initiation cue and during simple quiet standing revealed more significant responses in the former condition. Effects on the actual gait initiation process included shortening of the imbalance phase, larger backward/lateral displacement of CoP and more physiological expression of the underlying anticipatory muscular synergy. Additional changes were shortening of the unloading phase, shortening of the first-swing phase and increase in the length of the first step. Results demonstrate substantial influence of STN stimulation on functionally basic motor control mechanisms. In particular, the evidence of more significant responses upon attention-demanding conditions and the remarkable effects on postural programmes sub-serving feed-forward regulation of the onset of complex multijoint movements, suggests a consistent action on postural subsystems relying on cognitive data processing and internal models of body mechanics.

Keywords Deep brain stimulation · Subthalamic nucleus · Initiation of gait · Anticipatory postural adjustments · Parkinson's disease

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Introduction

Chronic electrical stimulation of deep brain structures belonging to the basal ganglia, such as motor thalamus, globus pallidus (GP) and more recently subthalamic nucleus (STN) is known to effectively ameliorate the motor performance in Parkinson's disease (PD; Benabid et al. 1991; Siegfrid and Lippiz 1994; Limousin et al. 1995; Kumar et al. 1998; Hallet and Litivan 1999; Thobois et al. 2002). Thalamic stimulation in the ventral intermediate nucleus (Vim) can markedly improve contralateral tremor, whereas GP and STN are effective targets for reducing rigidity and akinesia, with the STN stimulation reportedly entailing more consistent antikinetic effects, greater reduction of associated antiparkinsonian medication and lower requirement of stimulus intensity (e.g. Volkmann 2004). High-frequency (>100 Hz) stimulation of STN, in particular, proved to affect a number of functional actions involving lower limbs (walking), upper limbs (proximal and distal motor tasks including handwriting) and cephalic body segments (speech). Improvement of steady-state treadmill and overground ambulation was shown to be dramatic, pertaining to stride dimensions (increased step length and/or increased cadence; Allert et al. 2001; Krystkowiak et al. 2003), trunk kinematics (axial verticalization; Ferrarin et al. 2004), lower limb

joint kinematics (enhanced angular and segment excursions; Faist et al. 2001; Ferrarin et al. 2002) and joint dynamics (normalization of moments and powers; Ferrarin et al. 2005). Reported benefits on the upper limb function were consistent for slow ramp arm movements, ballistic forearm movements and isometric contractions of the forearm muscles (increased velocity and force production); however, they were rather modest for tasks implying skilled wrist/hand actions (mild increase in velocity for grasping, tapping and peg-board test, and improved smoothness and stroke length for handwriting; Brown et al. 1999; Siebner et al. 1999; Wenzelburger et al. 2003). Changes in the speech pattern were shown to be even less obvious (minor increase in the sound pressure level and fundamental frequency variability; Dromey et al. 2000; Krack et al. 2003) or negative (impairment in verbal fluency; Shroeder et al. 2003).

According to the current evidence, therefore, interfering with STN activity in PD patients by high-frequency electrical stimulation appears to influence a wide spectrum of motor tasks, but tends to affect preferentially the axial, proximal and locomotion-related movements, i.e. those controlled by relatively lower hierarchical levels of the motor system. Despite the physiological and clinical relevance of this notion, the effects of STN stimulation on functionally basic aspects of motor control, and particularly the impact on the different modes of postural control, have received partial attention. Although stimulation-induced changes in the body sway and reactive compensations to destabilizing perturbations have been investigated in some detail (Maurer et al. 2003; Rocchi et al. 2004), no specific study has been devoted so far to the effects of STN stimulation on predictive postural mechanisms operating prior to or simultaneously with the initiation of voluntary movements. Depending on the intended movement, these anticipatory postural adjustments (APA) are aimed at stabilizing (e.g. during fast arm raising performed while standing) or destabilizing (e.g. during the gait initiation process) the position of a given set of body segments for the subsequent execution of functionally optimized actions (e.g. Bouisset and Zattara 1981; Massion 1992; Crenna et al. 1991). APA are believed to involve neural systems sharing common structures with the basal ganglia output targets and are known to be consistently impaired in patients with PD (Bazalgette et al. 1986; Lee et al. 1995; Gantchev et al. 1996; Burleigh-Jacobs et al. 1997), either depending on changes in the background antigravitary postural set or incorrect structuring of temporo-spatial parameters of the underlying motor programmes (Crenna et al. 1990). To elucidate the effects of STN on the anticipatory adjustments associated with the initiation of one of the functional actions most frequently impaired in PD, we sought to analyze the transition from upright standing to steady-state walking, in a group of PD patients undergoing therapeutic deep brain stimulation.

Methods

Subjects

Ten patients with idiopathic PD and ten sex-/age-matched controls voluntarily took part in the study, by giving written informed consent to the protocol approved by the local Ethical Committee. The study conformed to the declaration of Helsinki. Demographic and anthropometric data are presented in Table 1.

All patients had undergone surgery at the Department of Neurosurgery, C.T.O. Hospital, Turin, 10.4 ± 7.0 months before the recording session and were currently receiving chronic deep brain stimulation through multicontact electrodes implanted bilaterally in the STN. Inclusion criteria for surgery were: diagnosis of idiopathic PD (Gelb et al. 1999), good response to levodopa (at least 30% improvement in unified Parkinson's disease rating scale (UPDRS) motor score with a levodopa dose 1.5 times higher than the usual first morning dose) in the presence of severe drug-related motor complications (motor fluctuation and dyskinesias) and absence of relevant NMR abnormalities, dementia, psychosis and severe depression. An additional selection criterion for the present study was the capability of walking at least for 5 m without aid, both in the medication off and stimulation off conditions. During operation (procedure described in detail in Lopiano et al. 2001), electrophysiological recordings and stimulation were used to locate the STN. Correct electrode positioning was confirmed after surgery by magnetic resonance imaging (MRI). Electrode contacts were tested in the absence of antiparkinsonian treatment, using monopolar cathodic stimulation (pulse width 60 μs, frequency 130 Hz). The stimulus voltage was progressively increased from 0 to 6 V (0.5 V steps) and the contacts which yielded a clinical response with the lowest voltage and highest side-effect threshold were selected for chronic stimulation. The optimum pulse width was also identified and levodopa dosage concurrently decreased. At the time of the study, the mean amplitude of stimulation was 3.1 ± 0.4 V, the mean frequency 143.3 ± 17.4 Hz and the pulse width 60 μs in 60% of the electrodes and 90 μs in the remaining 40%. The mean daily levodopa-equivalent dosage was 1,102.5 in the pre-operative period and 300 at the time of the study. No significant changes in neuropsychological assessment were observed in the follow-up.

Table 2 details the clinical profile of motor involvement in the group of PD subjects, assessed by the UPDRS part III, at the time of the study. In the absence of medication and STN stimulation (M-S-), the severity score range was 15–31.5 for akinesia (UPDRS III items 23, 24, 25, 26, 31) and 11–19 for rigidity (UPDRS III, item 22). Tremor (UPDRS III items 20, 21) was mild in five patients and severe in the others. Motor involvement was rather symmetrical in that the largest difference between the right and left side was 28, 20 and 25% of

Table 1 Subjects' characteristics at the time of the study

Patient	Age (years)	Sex	Height (cm)	Weight (kg)	Duration of disease (years)	Time post-surgery (months)	H&Y score stimulation off	H&Y score bilateral stimulation
P1	57	F	160	64	14	14	4	2.5
P2	62	M	165	83	13	8	4	2
P3	52	F	170	62	26	13	4.5	3
P4	68	M	180	87	20	3	4.5	2.5
P5	60	M	182	80	14	8	3	2.5
P6	56	M	172	70	22	8	4	2.5
P7	57	M	175	83	8	4	4	2.5
P8	63	F	153	63	13	9	3	2.5
P9	66	F	160	78	17	9	3	2.5
P10	61	F	170	79	22	28	2.5	1.5
Mean	60.2		168.7	74.9	16.9	10.4	3.7	2.4
(SD)	4.8		9.3	9.3	5.5	7.0	0.7	0.4
Controls Mean	59.2		169.4	70.1				
(SD)	4.5		6.3	11.0				

Mean values and SD for patients and controls are reported in the bottom rows
H&Y Hoehn and Yahr scale

Table 2 Clinical features of the group of PD subjects assessed by unified Parkinson's disease rating scale motor score and sub-scores

	M-S-	M + S-	M-S +	M + S +
UPDRS III[a, b]	61.6 ± 10.9	24.4 ± 14.4	20.5 ± 10.1	13.2 ± 7.3
Akinesia (items 23, 24, 25, 26, 31)[a, b]	25.9 ± 5.1	10.4 ± 8.2	7.8 ± 4.7	5.0 ± 4.7
Rigidity (item 22)[a, b]	14.5 ± 2.8	5.9 ± 2.2	5.5 ± 2.7	3.3 ± 2.1
Tremor (items 20, 21) [a]	8.1 ± 6.3	1.5 ± 2.9	1.5 ± 1.9	0.2 ± 0.3
Postural stability (item 29)[a]	2.0 ± 0.6	1.6 ± 0.9	1.4 ± 0.6	1.4 ± 0.7
Gait (item 30)[a]	2.4 ± 0.9	0.9 ± 1.1	0.6 ± 0.5	0.4 ± 0.6

Mean values ± SD. M + (M-): medication on (off); S + (S-): bilateral STN stimulation on (off). Significant difference ($P < 0.05$) among conditions (paired Student's *t* test)
[a] M-S + versus M-S-
[b] M + S + versus M + S-

maximal unilateral score for akinesia, rigidity and tremor, respectively. All patients displayed significant gait impairment (UPDRS, item 30: 1 in one patient, 3.5 in two patients and 2–3 in the others) and seven of them reported freezing episodes. In all cases, both dopaminergic therapy (M + S-) and STN stimulation (M-S +) induced significant amelioration of motor scores, including postural and gait disturbances. Simultaneous administration of pharmacological treatment and STN stimulation (M + S +), moreover, revealed synergistic effect, witnessed by additional improvement in the global UPDRS performance, akinesia and rigidity and a trend toward amelioration in the individual motor subscores for postural instability and gait. Two patients still reported rare freezing phenomena.

Experimental protocol

The following protocol for the study of APA, designed to be completed within a 1-day session to avoid potential confounding effects of day-to-day variability, was applied to patients and controls. Subjects stood upright while looking in front of them at eye level, arms down at their sides and feet hip-width, and, after delivery of a verbal warning signal (''ready''), started walking at a natural (preferred) speed, as soon as they received a gait initiation verbal cue which specified which leg they had to start with (''right-go'' or ''left-go''). The time interval between the warning signal and the initiation cue was 10 s. In order to assess a possible influence of the attentional drive related to the expectation of the gait initiation cue on the standing posture and/or on the outcome of STN stimulation, additional trials were performed, in which subjects simply stood quietly upright with gaze, arms and feet in the reference position. Patients started the session in the morning, at least 12 h after withdrawal of antiparkinsonian medication and performed four sets of trials separated by time intervals of at least 60 min, during which they rested comfortably on a chair. Conditions were: (1) right and left side stimulation on (Srl +) (this was the chronic condition of the patients as they arrived to the lab and was always tested first to minimize the duration of the whole session by avoiding initial and post-trial washout phases); (2) right side stimulation on (Sr +) and (3) left-side stimulation on (Sl +); (4) stimulation off (S-). Conditions Sr + , Sl + and S- were counterbalanced among patients, who were always unaware of the current condition. For each condition, a set of five trials including a regular

upright standing and four gait initiation trials were performed featuring a mean recording time of 10 min. On two of the gait initiation trials, subjects stood with both feet on a force platform, to allow detection of the trajectory of the center of pressure (CoP), while on the other two they stood with only one foot (trailing limb) on the platform, to enable computation of joint moments of the first stance leg, from the ground reaction force acting on the single foot.

Set up and extraction of general parameters

Quiet standing and gait initiation were assessed by multifactorial analysis of kinematic, dynamic and electromyographic variables. Kinematic data were recorded according to the procedure reported in Ferrarin et al. (2002), using an optoelectronic system (ELITE, BTS, Milan, Italy), equipped with four video cameras, symmetrically located on both sides of the subject. Within a calibrated volume $2.5\times1\times2$ m^3, the three-dimensional position of subject's relevant body segments was determined by means of reflective markers 10 mm in diameter glued on the following bony landmarks: sacrum, seventh thoracic vertebra, seventh cervical vertebra and, on both sides of the body, posterior superior iliac spines, lateral femoral condyles, lateral malleoli and fifth metatarsal heads. After data acquisition (sampling frequency: 50 frames/sec), the marker coordinates were low-pass filtered (cut-off frequency 3–7 Hz) and individual anthropometric parameters were used to estimate the internal joint centers (Frigo and Rabuffetti 1998). These, in turn, enabled computation of trunk and lower limb kinematics. Ground reaction forces and CoP coordinates were measured by a dynamometric platform (Kistler, GmbH, Winterthur, Switzerland) embedded in the floor (sampling rate 50 Hz). The resulting signals were used for the calculation of the CoP trajectory and lower limbs joints moments. Surface EMGs were recorded using a telemetric 8-channel system (TELEMG, BTS, Milan, Italy) from tibialis anterior (TA), gastrocnemius medialis (GAM), rectus femoris (RF) and semimembranosus (SM) muscles of both legs. Myoelectric signals were collected by pre-amplified Ag/AgCl electrodes (diameter: 25 mm, bipolar configuration, inter-electrode distance: 20 mm), band-pass filtered ($f_{\text{high-pass}} = 10$ Hz, $f_{\text{low-pass}} = 200$ Hz) and acquired at a sampling frequency of 500 Hz and a resolution of 12 bit. A digital zero-phase shift eight-order Butterworth high-pass filter with a cut-off frequency of 20 Hz was applied in order to remove movement artifacts.

Extraction of specific parameters

The standing postural attitude was characterized by the following set of parameters: mean forward inclination of trunk, thigh and shank in the sagittal plane (computed as the angle between each segment and the vertical direction; positive value: forward), mean CoP displacement in the antero/posterior (A/P) direction (normalized to the distance between lateral malleolar and fifth metatarsal marker; 0: intermalleolar point, positive values: forward) and medio/lateral (M/L) direction (normalized to the inter-malleolar distance, positive values: towards left foot for quiet standing, towards trailing foot for standing preceding gait initiation), mean hip, knee and ankle joints moments in the sagittal plane and root mean square (RMS) value of the EMG signals recorded from TA, GAM, RF and SM muscles. RMS was computed on the rectified myoelectric signal, as $\sqrt{\Sigma x_i^2}/n$, where $i = 1,\ldots,n$; and n is considered as the time window. The latter lasted at least 1,000 ms, and for the gait initiation trials it was identified on the EMG activity which preceded the first sign of gait initiation synergy (onset of GAM inhibition or increase of TA activity).

The gait initiation phase was analyzed with reference to three functional sub-periods, based on the path travelled by the CoP before the leading (swing) limb completed the first step: (1) the imbalance phase, characterized by initial displacement of the CoP backward and toward the future leading foot; (2) the unloading phase, marked by lateral displacement of the CoP back toward the future trailing (stance) foot; (3) the first swing, characterized by forward progression of the CoP under the trailing foot, from the toe-off to the heel-strike of the leading leg. Accordingly, six temporal markers were automatically computed by a dedicated algorithm and checked by visual inspection through an interactive software: (1) onset of the anticipatory postural adjustment phase (APA onset); (2) heel-off of the leading foot (the foot which performs the first step; HO_{ld}); (3) toe-off of the leading foot (TO_{ld}); (4) heel-strike of the leading foot (HS_{ld}); (5) toe-off of the trailing foot (TO_{tr}) and (6) heel-strike of the trailing foot (HS_{tr}). The procedure for their calculation is shown in Fig. 1. Once the temporal instants were determined, the following set of parameters were measured: duration of the imbalance phase (APA onset—HO_{ld}), backward shift of CoP at HO_{ld} (normalized to the distance between lateral malleolar and fifth metatarsal marker), CoP shift toward the leading foot at HO_{ld} (normalized to the inter-malleolar distance during standing), duration of the unloading phase (HO_{ld}–TO_{ld}), duration of the first swing (TO_{ld}–HS_{ld}), length of the first step (normalized to subject's height), average velocity of the leading foot during the first swing phase, maximal vertical displacements of the leading foot malleolus and fifth metatarsal head during first step, velocity of the sacrum marker at HS_{tr} (considered as the steady-state progression velocity as shown in Brénière and Do 1986).

Statistical analysis

For each subject and condition, all variables have been averaged over the four gait initiation trials. Moreover, for variables related to lower limbs (angles, joint

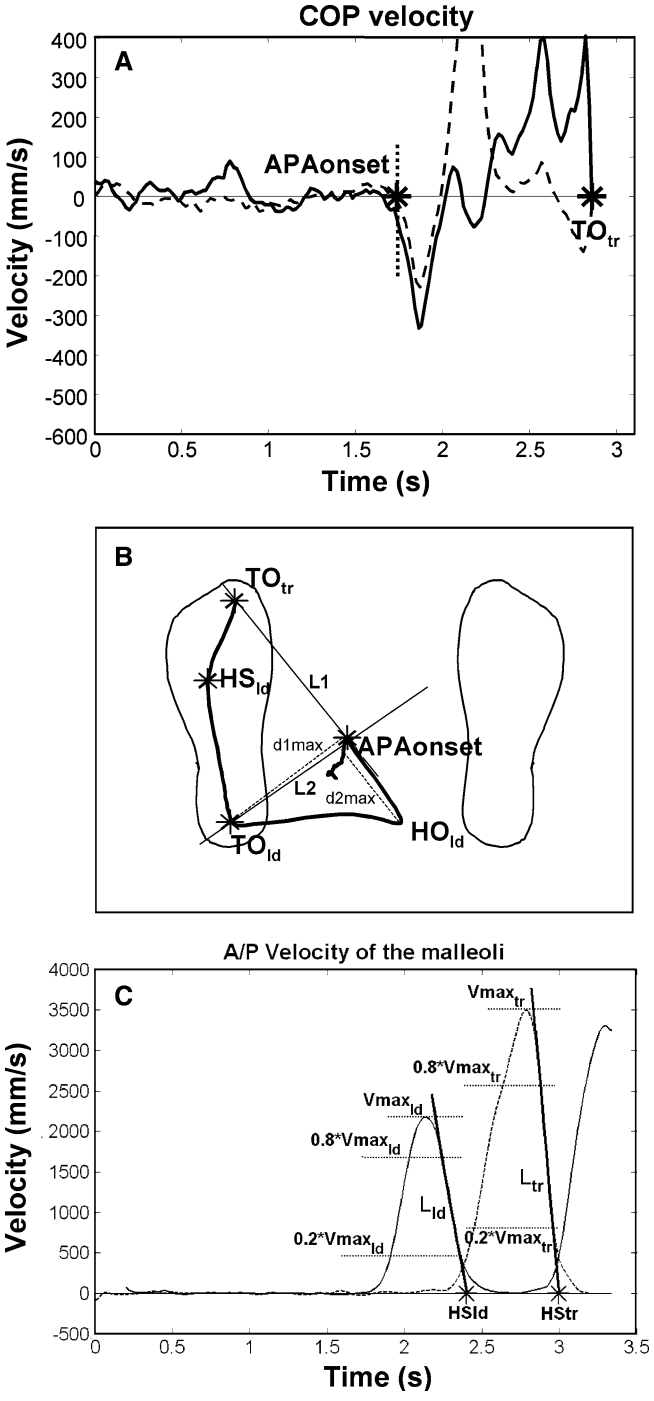

Fig. 1 Procedures for automatic computation of temporal markers for the analysis of the gait initiation process. **a** The *instant of APA onset* was identified from the platform signals as the first frame in which both components of the profile of CoP velocity (*solid line*: A/P velocity, forward-directed; *dashed line*: M/L velocity, directed toward the trailing foot) were negative. The toe-off of the trailing limb (TO_{tr}) was identified as the last frame of the force platform signal. **b** CoP displacement in the M/L and A/P directions. The toe-off of the leading limb (TO_{ld}) was identified as the frame in which the position of CoP attained the maximal distance (d1max) from the line (L1) passing through the two points representing the CoP position at APA onset and TO_{tr}. The heel-off of the leading limb (HO_{ld}) was computed as the instant at which the CoP position attained the maximal distance (d2max) from the line (L2) passing through the two points representing the CoP positions at APA onset and TO_{ld}. **c** The instants of the heel-strikes of the leading and trailing limb (HS_{ld} and HS_{tr}) were detected from the A/P velocity of the malleolar markers of the leading (*solid line*) and trailing foot (*dashed line*), as the frames in which the two lines L_{ld} and L_{tr} reached the zero values. L_{ld} and L_{tr}: *interpolation lines* of the velocity values within the range $0.2Vmax_{ld}$–$0.8Vmax_{ld}$ and $0.2Vmax_{tr}$–$0.8Vmax_{tr}$, belonging to the portion of signals with negative slope (deceleration of the malleoli)

moments, RMS values) left- and right-side values have been considered separately. The difference between the control and the PD group under stimulation off condition was analyzed using a two-tailed Student's *t* test for each variable. Then, differences among the three conditions (basal, unilateral and bilateral STN stimulation) were assessed by means of repeated measures analysis of variance (ANOVA). Data normality was checked using Shapiro–Wilk's *W* test. The level of significance was set at 0.05 and, whenever the ANOVA procedure revealed significant differences, post hoc comparisons were performed using the Student–Newman–Keuls test.

Results

Analysis of the effects of STN stimulation on the initiation of gait will be presented in two sections dealing with the standing phase preceding the delivery of the gait initiation cue and the actual gait initiation process, respectively.

Initial standing posture

While patients were waiting for the gait initiation cue under basal (stimulation off) conditions, the distribution of the weight support in the frontal plane, as monitored by the CoP, was not significantly different from age-matched controls, whereas noticeable postural abnormalities were detected in the sagittal plane (Table 3). These included augmented forward inclination of the trunk, increased inclination of the thigh and shank with respect to vertical, anterior shift of the CoP under the support base and increased external moments of force at the hip and knee joints. Since no significant differences were found between right and left limb, data have been pooled together in Table 3. A single-subject multifactorial analysis allowed recognition of two main postural profiles, in which the forward inclination of the trunk was greater (type I profile, four subjects) or lower (type II profile, six subjects), as compared with the inclination of the thigh and shank, respectively (Fig. 2a). Over the time window adopted for kinematic and kinetic analysis, the resting EMG activity from the four muscles tested was higher in patients (average RMS 22.1 ± 16.0 vs. 11.4 ± 11.7, $P = 0.0000$), with larger values in the flexor (SM–TA) (ratio RMS patients/RMS controls = 2.69) as

Table 3 Kinematic and dynamic parameters characterizing the standing posture preceding delivery of the gait initiation cue in the control and in the PD subjects under stimulation off condition

	Controls		PD stimulation off		*P* value
	Mean	SD	Mean	SD	
Trunk forward inclination (°)	4.9	3.0	15.0	7.1	0.0006*
Thigh forward inclination (°)	1.6	3.7	14.1	7.9	0.0000*
Shank forward inclination (°)	−7.5	2.8	−11.6	3.0	0.0000*
COP M/L (normalized)	3.0	4.1	8.0	10.2	0.1668
COP A/P (normalized)	59.5	11.6	73.8	14.7	0.0322*
Hip moment (Nm/Kg)	0.032	0.124	0.336	0.173	0.0000*
Knee moment (Nm/Kg)	0.006	0.099	0.116	0.136	0.0071*
Ankle moment (Nm/Kg)	0.343	0.103	0.348	0.109	0.9017

Sign convention for angles is shown in Fig. 2
*Significant differences between the two groups ($P < 0.05$)

compared to extensor muscles (RF-GAM; ratio RMS patients/RMS controls = 1.53). This phenomenon was in part due to a low-frequency tremor (4.5–5.5 Hz), preferentially affecting the flexor groups (TA: 9 limbs; SM: 1 limb; GAM: 3 limbs).

The aforementioned postural abnormalities were consistently improved by STN stimulation. Changes were qualitatively similar upon unilateral and bilateral stimulation, but were more robust in the latter condition. Moreover, no significant differences were detected between unilateral stimulation applied to the right and left STN, and between the effects on the sides ipsi- and contralateral to stimulation (only one subject showed a trend to more consistent contralateral effects), so that results from both types of unilateral stimulation and both sides of the body were grouped together. As indicated in Fig. 2b and in the graphs reported in Fig. 3, effects of STN stimulation on the standing posture included: reduction of the forward trunk bending (n.s., unilateral and $P = 0.0065$, bilateral), trend toward a lower inclination of the thigh and significant decrease of the inclination of the shank ($P = 0.0009$ unilateral; $P = 0.0001$ bilateral). Kinetic counterparts of the previous figures were reduction of the mechanical moment at the hip (n.s. unilateral; $P = 0.0102$ bilateral) and ankle (n.s. unilateral; $P = 0.0102$ bilateral) and backward shift of the CoP ($P = 0.0142$ unilateral; $P = 0.0016$ bilateral). As for the EMG changes, the global motor output from the four muscles tested was significantly reduced ($P = 0.0099$ unilateral, $P = 0.0030$ bilateral), with a similar effect on extensor (n.s. unilateral, $P = 0.0276$ bilateral) and flexor groups ($P = 0.0141$ unilateral, $P = 0.0319$ bilateral). Moreover, in patients exhibiting lower limb tremor (four patients bilaterally, two patients unilaterally) the RMS values of the affected muscles were significantly decreased ($P = 0.0122$ unilateral, $P = 0.0065$ bilateral).

To assess whether the attention-demanding condition associated with preparation to move in response to an external cue might influence the standing postural profile and/or the effectiveness of STN stimulation, additional recordings were made in which patients were asked to maintain a regular standing posture, in the absence of STN stimulation and in the presence of bilateral STN stimulation. Results indicate that, in the stimulation off condition, the orientation of the main body segments,

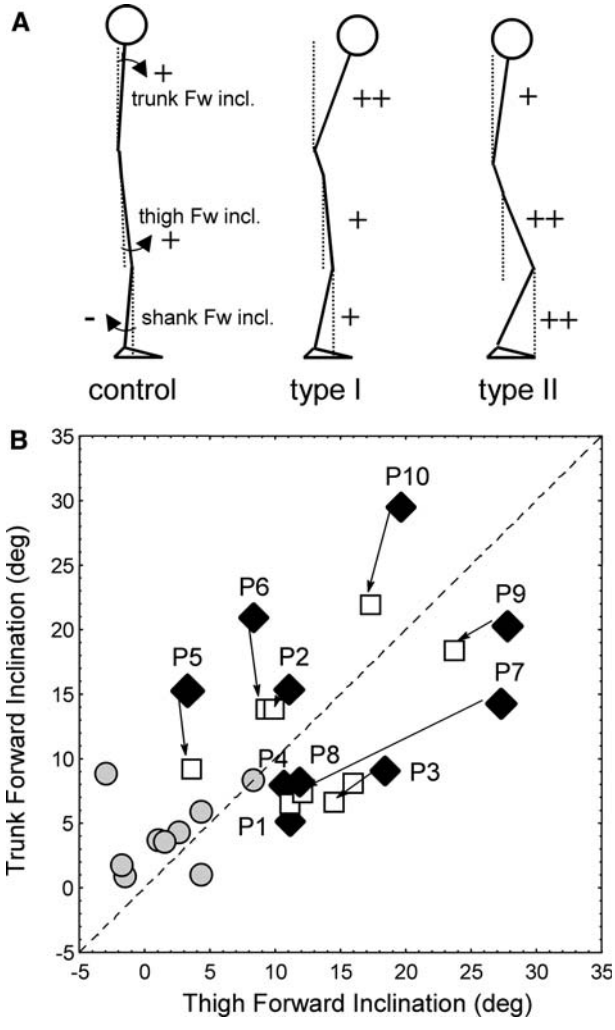

Fig. 2 **a** Standing postural profiles expressed by healthy controls and PD subjects, characterized by absolute angular parameters of trunk and thigh. **b** In the graph, the forward inclination of the trunk is plotted versus the forward inclination of the thigh with respect to the vertical, in the sagittal plane. *Gray circles, black diamonds and white squares* indicate controls, PD patients under stimulation off conditions and PD patients upon bilateral STN stimulation, respectively. *Diamonds* located over and under the diagonal refer to patients exhibiting type I and type II postural attitude, respectively. Note that STN stimulation shifts parameters toward the reference values (*arrows*)

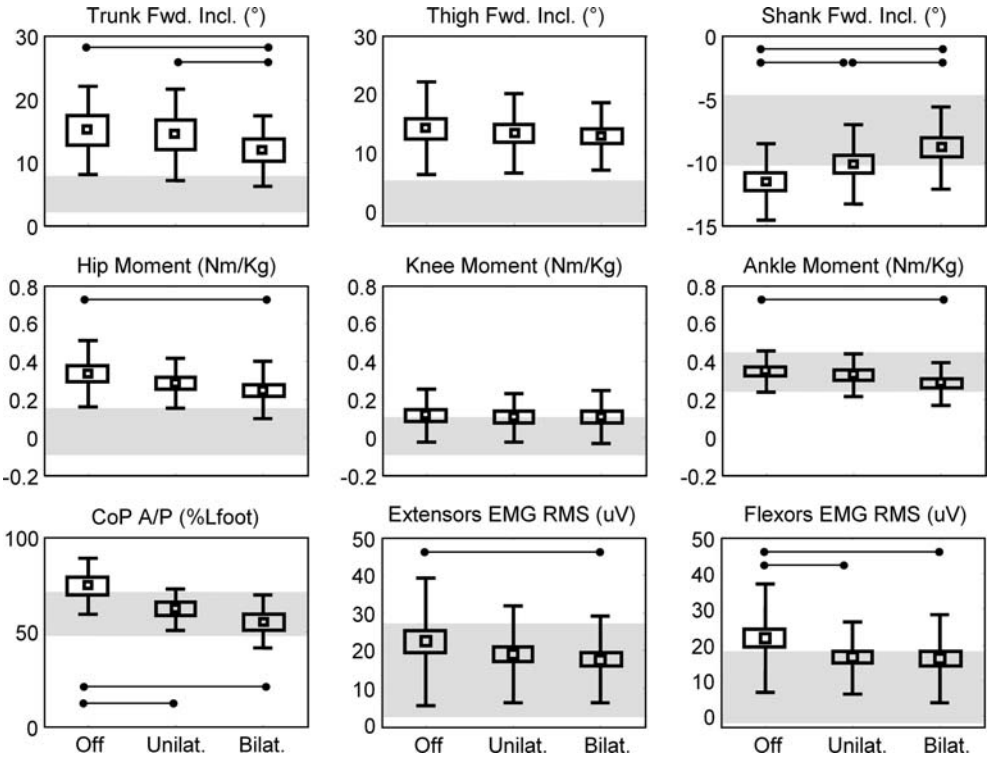

Fig. 3 Descriptive parameters of the standing posture in the control subjects and PD subjects under stimulation off, unilateral STN stimulation on and bilateral STN stimulation on conditions. Means (*bold squares*), SE (*boxes*), SD (*whiskers*) are shown for each condition. ±1 SD band from control subjects is shown in *gray*. *Horizontal lines and dots* indicate significant differences ($P < 0.05$)

the related kinetic parameters and the global EMG levels were not significantly different when patients were quietly standing and standing while waiting for the gait onset cue, although trends toward higher EMG recruitment in the extensor and flexor muscles were observed in the latter condition. Upon STN stimulation, however, effects were more significant during the standing phase which preceded the gait initiation cue. Higher consistency involved the forward inclination of the trunk ($P = 0.0409$ simple standing vs. $P = 0.0213$ standing prior to gait initiation), the inclination of the shank ($P = 0.0608$ vs. $P = 0.0000$), the antero-posterior position of the CoP ($P = 0.5706$ vs. $P = 0.0083$) and the absolute values of the resting EMG amplitudes, both in the extensor ($P = 0.4058$ vs. $P = 0.0445$) and flexor ($P = 0.5777$ vs. $P = 0.0416$) groups.

Initiation of gait

The initiation of gait was analyzed with reference to the imbalance, unloading and first swing phases (see Methods).

As shown in Fig. 4, where the instantaneous direction of the CoP pathway and the CoP speed were color-coded, the progressive transition from the imbalance phase (red and magenta), through the unloading phase (yellow), to the first swing phase (green), as well as the relative duration of the three sub-periods, were largely variable and irregular in patients under basal conditions, to become more consistent with unilateral STN stimulation and eventually quite close to the control template with bilateral stimulation. Directional abnormalities of the CoP path were mainly related to (1) absence or relative shortening of the initial posterior shift directed to the leading-leg, (2) anticipation or relative shortening of the subsequent lateral shift directed to the trailing-leg, and (3) presence of atypical sequences of lateral and forward displacements directed to the trailing-leg.

Quantitative analysis of relevant temporo-spatial parameters of the gait initiation process revealed that unilateral stimulation produced similar kinematic and kinetic effects on the initiation of gait obtained with the foot ipsilateral and contralateral to the stimulated side, so that these data were pooled together. As shown in the graphs reported in Fig. 5, with stimulation on, the imbalance phase was significantly reduced in duration ($P = 0.0324$ unilateral, $P = 0.0469$ bilateral stimulation), when present also in basal condition, while, when absent, it tended to be restored. At the same time, both the lateral and backward displacements of the CoP were clearly augmented, with higher consistency upon bilateral ($P = 0.0196$ lateral shift; $P = 0.0002$ backward shift), as compared to unilateral stimulation (n.s. lateral shift, $P = 0.0086$ backward shift). The subsequent unloading phase was significantly shortened as well (n.s. unilateral, $P = 0.0284$ bilateral stimulation). Likewise, the first step became longer ($P = 0.0403$ unilateral, $P = 0.0009$ bilateral stimulation) and faster ($P = 0.0195$ unilateral; $P = 0.0006$ bilateral stimulation). Foot lifting associated with the first swing phase showed non-significant changes when computed from the vertical excursion of the lateral malleolus ($P = 0.3196$ unilateral, $P = 0.5512$ bilateral stimulation), but proved to be significantly

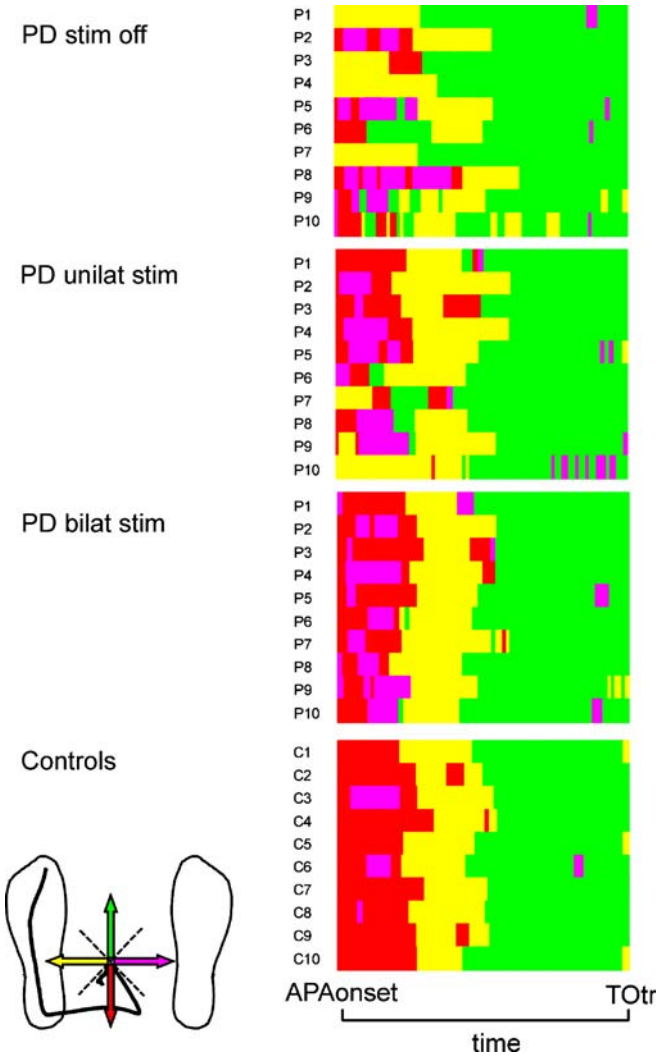

Fig. 4 Global analysis of the CoP pathway at the initiation of gait in PD patients (basal conditions, unilateral and bilateral STN stimulation) and in the control subjects. Each multi-colored horizontal bar refers to one subject and, for sake of clarity, to one representative trial. Instantaneous displacements of the CoP pathway were color coded according to the movement direction: posterior (*red*), anterior (*green*), toward the leading foot (*magenta*) and toward the trailing foot (*yellow*). *Time axis* represents the normalized time between APA onset and TO_{tr}

enhanced when measured from the vertical excursion of the forefoot (fifth metatarsal head; n.s. unilateral, $P = 0.0005$ bilateral stimulation), indicating a prominent effect of STN stimulation on the ankle joint excursion.

Further assessment was made of the motor programme underlying the main actions of the gait initiation process in the antero-posterior direction (the imbalance synergy), represented in the leg muscles by inhibition of the tonic postural activity of the triceps surae, followed by activation of the antagonist TA (Fig. 6). Under basal conditions, this synergy was severely abnormal in nine out of ten PD subjects. In particular, inhibition of GAM was absent in four subjects and revealed obvious abnormalities in the spatial (just detectable motor unit de-recruitment replacing the normal EMG silence) and/or temporal parameters (durations lower than 50 ms) in the remaining five subjects. The activation of TA was absent in three subjects, inconstantly present, reduced in amplitude or largely desynchronized in four subjects and segmented (i.e. made up by a sequence of small amplitude bursts) in one subject. Upon bilateral STN stimulation, striking changes in the imbalance synergy with restoration of near normal features were observed in three subjects, moderate changes in three subjects and no changes in four subjects. The most remarkable effects concerned the recovery of a silent period on GAM and/or the appearance or reinforcement of the typical burst on TA. The latter could reveal a segmented profile, when a standing TA tremor persisted during STN stimulation (Fig. 7 a, b) or a normally rich motor unit recruitment, when TA hyperactivity was absent (Fig. 7 c, d) or abolished by STN stimulation. Subjects displaying striking or moderate changes in the EMG profiles of the leg muscle showed more significant improvement of mechanical parameters related to the imbalance phase (e.g. backward and lateral CoP shifts) as compared to those related to the first swing phase (e.g. forefoot lift, and length and velocity of the first step), whereas subjects exhibiting unchanged imbalance synergies upon STN stimulation showed the opposite trend. Such an instrumentally detected difference was not evident on the UPDRS motor scores.

The changes described in the gait initiation process were paralleled by significant increments of the gait speed, measured at the heel-strike of the trailing limb, with a progressive displacement toward the reference range on moving from unilateral ($P = 0.0253$) to bilateral STN stimulation ($P = 0.0009$).

Discussion

We have shown that stimulation of STN can substantially influence the gait initiation process in patients affected by PD. Significant changes with respect to basal conditions were usually evident upon both unilateral and bilateral stimulation, but were typically more consistent with the latter. Although presentation order of unilateral trials was counterbalanced among subjects, bilateral stimulation trials were always administered first (see Methods), so that the possibility that changes in fatigue level and/or attentional drive throughout the session had a role in the different responsiveness of patients in the two conditions cannot be excluded. However, adoption of resting intervals as long as six times the actual duration of the recording phases (60 min at least vs. 10 min) is likely to have minimized the intervention of fatigue phenomena, and, along with the readiness cue provided by the experimenter prior to each go signal, to have enabled sustained allocation of attention during task executions. It should also be noticed that a potential advantage of bilateral stimulation trials related to

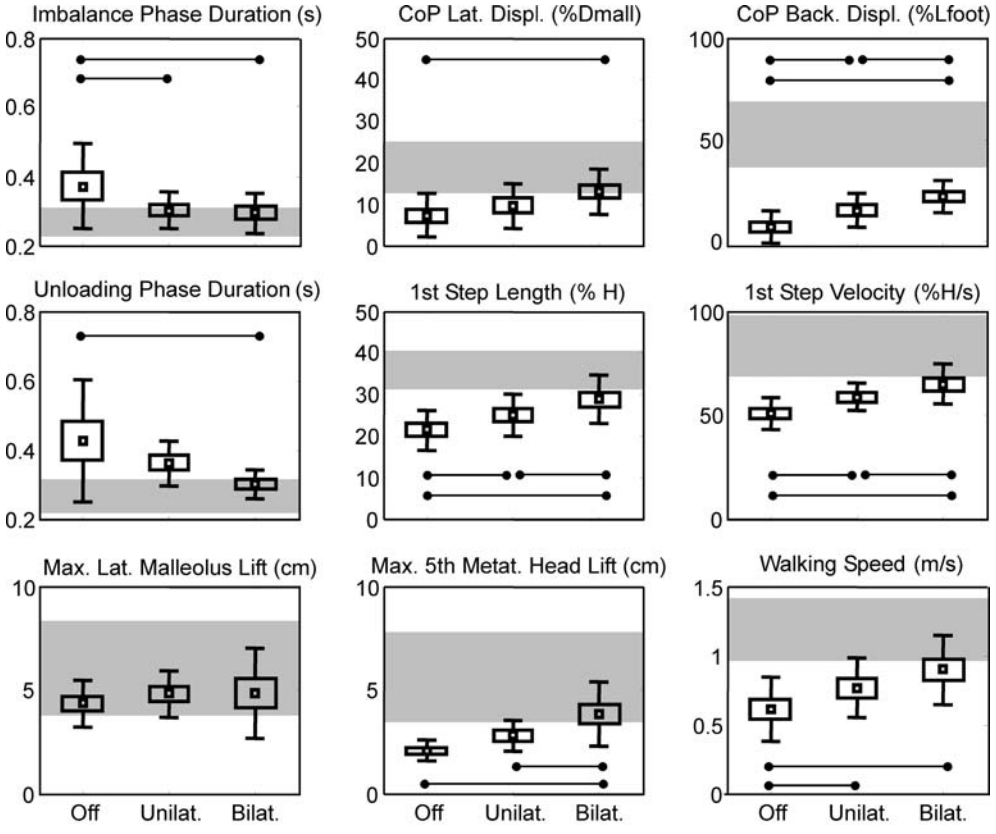

Fig. 5 Descriptive parameters of the gait initiation process in the control subjects and PD subjects under basal conditions, unilateral STN stimulation and bilateral STN stimulation. Means (*bold squares*), SE (*boxes*), SD (*whiskers*) are shown for each condition. ±1 SD band from control subjects is shown in *gray*. *Horizontal lines and dots* indicate significant differences ($P < 0.05$). Percentage of H = Percentage of subject height. Percentage of Lfoot = Percentage of the distance between lateral malleolar and fifth metatarsal marker. Percentage of Dmall = Percentage of inter-malleolar

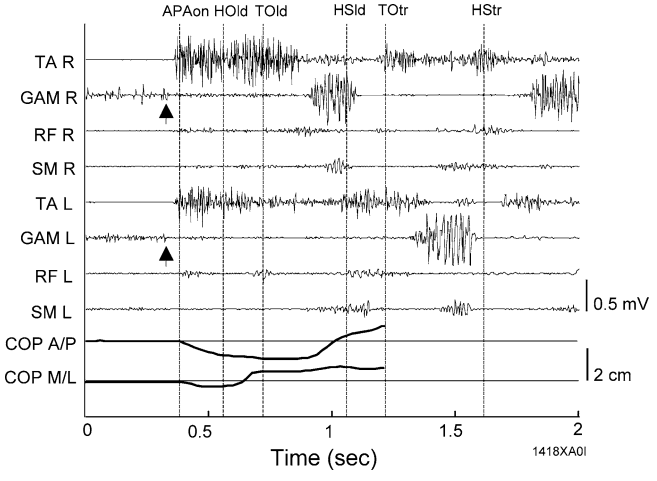

Fig. 6 EMG activity in the lower limb muscles and CoP displacement in the A/P (>0 forward) and M/L (>0 toward the trailing foot) directions recorded at the initiation of gait in a control subject. *Arrows* indicate bilateral suppression of the tonic activity of the GAM muscles which, along with the subsequent activation of the antagonist TA, represent the distal components of the imbalance synergy responsible for the backwards CoP shift. This, in turn, will start the forward fall of the body associated with the execution of the first step

earlier administration might have been balanced by a potential advantage of unilateral stimulation trials, related to a practice effect built up by repetitive execution. For the earlier reasons, in line with conclusions of other studies contrasting the impact of double- and single-side STN stimulation on axial and locomotor symptoms of PD (Kumar et al. 1999; Bastian et al. 2003), we suggest that the relatively improved responsiveness observed upon bilateral stimulation should be mainly ascribed to an additive effect

The main actions documented in the present study during STN stimulation involved three different components of the gait initiation process: (1) maintenance of the initial standing posture, (2) activation of the APA responsible for the forward body fall associated with the first step, and (3) actual execution of the first step. As for the standing posture, the abnormal orientation of the main body segments observed under basal conditions (augmented trunk, thigh and shank inclination with respect to the gravitational axis), the related kinetic profile (forward shift of CoP, and increased hip and knee joint moments) and the anomalous tonic and/or rhythmic myoelectric activity in the thigh and leg muscles, represent quantitative descriptors of the typical flexed attitude expressed by subjects with PD (e.g. Knuttson and Mårtensson 1986; Crenna et al. 1990). The earlier postural profile underwent remarkable changes upon STN stimulation, including correction of abnormal angular and force-related parameters, as well as depression of tonic and/or tremor activity in the lower limb muscles. An interesting finding in this context was that changes in the trunk bending, shank inclination and backward shift

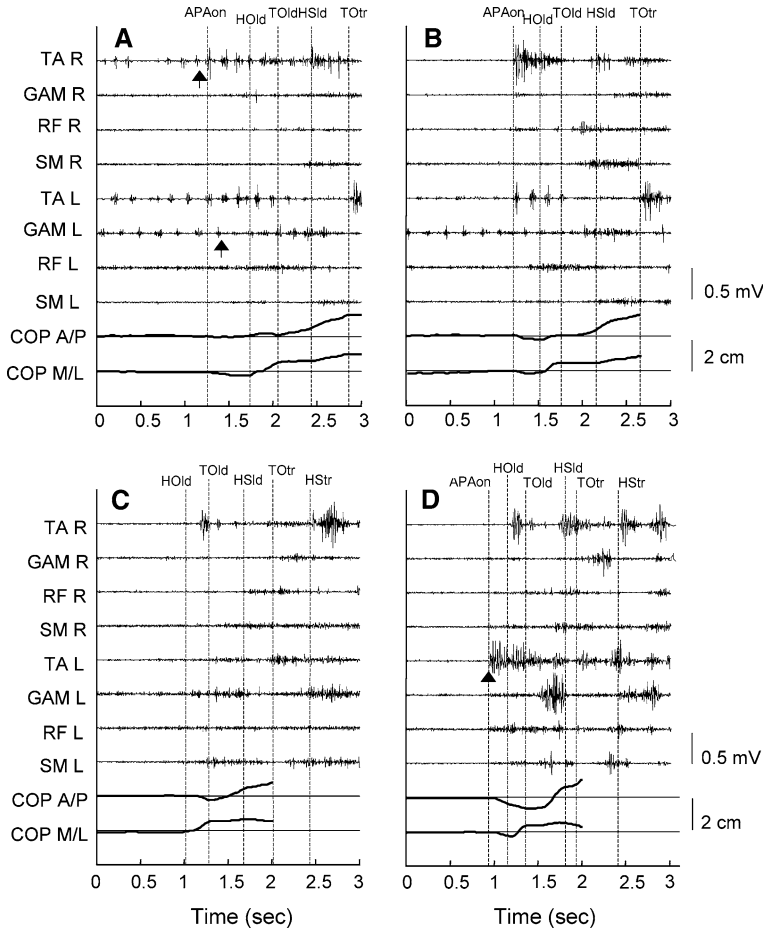

Fig. 7 EMG pattern and CoP displacement at the initiation of gait in a PD subject under basal conditions (**a**) and during stimulation of the left STN (**b**). In the absence of stimulation, a moderate increase in the amplitude of the tremor bursts on both TA and a subsequent depression of the tremor in the left GAM (*arrows*) identify the abnormal imbalance synergy. Mechanical ineffectiveness of such a motor pattern is documented by the absence of backward CoP shift (see A/P direction). Upon left STN stimulation, tremor is abolished on the right (contralateral) TA and attenuated on left TA. Moreover, bilateral activation of TA (a rich burst contralateral and a segmented recruitment ipsilateral to the stimulated STN) is conspicuous. Note the backward shift of CoP, which indicates a recovery of mechanical effectiveness of the imbalance synergy. Note also that the duration of the different subperiods of the gait initiation process is shortened upon stimulation as compared with the basal conditions. EMG activity in the lower limb muscles at the initiation of gait in a PD subject under basal conditions (**c**) and during bilateral STN stimulation (**d**). Note the appearance of a TA burst (*arrow*) on the left side, along with a near-normal profile of backward CoP displacement

of CoP attained higher statistical significance when subjects were waiting for the gait initiation cue, as compared with a simple quiet standing condition. Likewise, STN stimulation induced significant decrease in the baseline EMG hyperactivity when delivered prior to gait onset, but non-significant changes when applied during regular standing. This suggests that the attentional allocation associated with preparation to move in response to external cues might represent a behavioral substrate yielding more effective action by STN stimulation. A corollary of this concept would be that the contribution of abnormal STN activity to the anti-gravity postural control in patients with PD might become more relevant when the operational context implies cognitive data processing.

The improved orientation of the trunk induced by STN stimulation confirms similar effects reported for steady-state walking (Ferrarin et al. 2004), but demonstrates an action on the axial tone also when postural mechanisms operate in the foreperiod preceding externally cued movement initiation or even independently from intentional movements. Bilateral STN stimulation restored a near-normal inclination of the body segments with respect to the gravitational vertical, independently of the type of current standing posture. When trunk inclination was higher than thigh and shank (type I standing posture), stimulation yielded a more erect trunk attitude, whereas when thigh and shank inclination exceeded the trunk (type II standing posture), the effect was a better alignment of lower limb segments. This figure is compatible with a global action on the anti-gravity postural set, involving more selective distribution of basic postural commands between metameric trunk and lower limb extensor muscles. In

agreement with the present observations, Maurer et al. 2003, in a study of PD subjects undergoing STN stimulation, reported reduction of the mechanical coupling between trunk and hip segments (i.e. in the axial stiffness) during quiet stance.

Restoration of a physiological inter-segmental relationship during standing was coupled with a shift of the CoP back toward the control values. The earlier improved kinetic conditions, however, are not necessarily paralleled by recovery of the equilibrium control, as shown by standard posturographic measures. In fact, along with significant decrease in the sway amplitude during quiet stance (Rocchi et al. 2004), increased sway has been described as well as upon STN stimulation (Maurer et al. 2003). Moreover, STN stimulation was shown to have little influence on the defective compensation against external destabilizing perturbations (platform tilt and displacement of the visual scene), which typically hinders postural maintenance in PD (Maurer et al. 2003). At variance with the anti-gravity tone, therefore, the control of equilibrium and reactive postural mechanisms does not seem to be always positively responsive to STN stimulation. Of interest, lower responsiveness to treatment of peripherally triggered postural control actions as compared to anti-gravity tone was described also for levodopa therapy (Horak and Frank 1996), suggesting that STN stimulation operates on the postural control, at least in part, through dopaminergic systems (see also Brown et al. 1999, 2004).

The conspicuous amelioration of the standing profile produced in patients by STN stimulation might account per se for beneficial effects on the gait initiation process. In fact, interaction of the motor commands responsible for the initial forward body fall (the imbalance programme) with abnormal baseline activity in the target muscles was shown to be one of the mechanisms accounting for deteriorated expression of the APA in PD (Crenna et al. 1990). As aforementioned, the imbalance synergy in the leg muscles comprises suppression of the tonic activity in the triceps surae, followed by activation of the antagonist TA (Brénière and Do 1987; Crenna and Frigo 1991; Fig. 6). Interaction of a virtually normal set of instructions for the recruitment of the TA component with ongoing oscillatory activity in the target motoneurons (TA tremor) will result in a desynchronized and prolonged TA burst, with possible degradation of the overall mechanical effectiveness (e.g. Fig. 7a). In this respect, suppression of the resting tremor by STN stimulation will bring about a more physiological expression of the imbalance programme. Evidence from animal studies indicates that an adequate postural support is a pre-requisite for a normal initiation and maintenance of locomotor behaviors, in that activation of the spinal locomotor networks by descending commands from the dorsal brainstem requires a threshold anti-gravity activity (Mori and Otha 1986). It is possible, therefore, that the resetting of postural profile observed upon STN stimulation might contribute to a more physiological activation of the gait initiation programme. In the same vein, the observation that initial limb geometry, i.e. the relative angular relationship between limb segments, can influence the pattern and timing of the onset of locomotion (Bonnot et al. 1996) might suggest that restoration of a correct alignment of trunk and limb segments promoted by STN stimulation might play a role in the amelioration of the gait onset in PD patients.

The evidence of stimulation-dependent recovery of near-normal gait initiation in patients exhibiting minor postural deficits under basal conditions (e.g. subject in Fig. 7 c, d) indicates that STN stimulation can act on the gait initiation process by affecting targets other than basic postural tonogenic systems. Indeed, in a study of the pathophysiology of gait initiation (Crenna et al. 1990), it was shown that the very imbalance programme can be severely impaired in PD. Pathological changes were related to (1) temporal down-scaling, i.e. overall prolongation of the inhibitory and excitatory EMG components and increase in their relative delay, as well as to (2) disorganization (e.g. inversion of onset times), defective expression or even loss of one or both components. Similar abnormalities have been confirmed here under basal conditions. A novel finding of the present study was that stimulation of STN is able to restore the expression of the imbalance programme in the leg muscles. This action was obtained by yielding a clearer inhibition of triceps surae along with a more intense and synchronized EMG recruitment on TA and/or by resurrecting the missing components, most often on both sides. With reference to the main action of triceps surae and pre-tibial muscles in the sagittal plane, the resulting biomechanical effect was, as expected, a larger backward shift of the CoP, and, in turn, a higher forward acceleration of the whole body center of mass (Brénière et al. 1987; Crenna and Frigo 1991). Although muscles acting in the frontal plane were not recorded, the increase in the lateral CoP displacement observed upon STN stimulation indicates a parallel restoration of the components of the motor programme responsible for unloading the leading limb (which include activation of tensor fasciae latae; Carlsöö 1996). Altogether, these data demonstrate that the integrated set of APA exerted in the sagittal and in the frontal plane can be restored by STN stimulation, with a consequent optimization of the biomechanical pre-requisites for gait initiation.

Simultaneously with the positive effects on the APA, we have shown a stimulation-dependent improvement in the execution of the first step, either in terms of length, velocity or lift of the forefoot. In this respect, STN stimulation appears to provide a parallel recovery of (and possibly a linkage between) two sets of motor programmes: an initial set underlying the APA and a second set of programmes, more strictly locomotor, responsible for the swing and stance phases of the first step. Such an action might effectively counteract a higher-level pathophysiological mechanism which possibly underlies the disturbed gait onset in PD, i.e. the

impaired capacity of the central programming systems to appropriately operate over a sequence of motor programmes (Benecke et al. 1987; Crenna et al. 1990).

It is worth mentioning that the findings discussed previously refer to the short-term (mean 10.7 months) impact of STN stimulation on the initiation of gait in PD. A recent prospective study by Krack et al. (2003) demonstrated that 5 years after bilateral implantation of STN stimulating electrodes, UPDRS motor scores were still improved (by 54% on average with respect to the basal level), when assessed in the medication-off/stimulation-on state (M-S+), i.e. with the same protocol adopted in the present study. However, when evaluation was made during the period of maximal clinical benefit after administration of a suprathreshold levodopa dose, STN stimulation failed to potentiate the effects of the drug on motor symptoms such as postural stability and gait. The deterioration of the synergistic effects of STN stimulation and pharmacological therapy on the long term might be related to the natural history of PD, which implies progressively lower responsiveness to levodopa of a subset of axial signs (Krack et al. 2003). The possible partial action of STN stimulation through dopaminergic systems (see previous), would be consistent with such an hypothesis.

Although the present results cannot provide direct information about the neural structures mediating the effects of STN stimulation, a number of tentative propositions can be forwarded about the postural control systems potentially involved. These should take into account the documented connections of STN with structures related to the anti-gravity postural set, expression of APA, execution of the first step and harmonic sequencing and integration thereof. Based on mammalian and particularly primate hodology, candidates for the effects on the postural tone are the consistent connections which, via substantia nigra pars reticulata (SNr), allow the STN to gain oligosynaptic access to the tonogenic centers of the mesopontine tegmentum (Armstrong 1986; Mori et al. 1989; Pahapill and Lozano 2000; Takakusaki et al. 2003). Less likely are the direct connections between STN and the tonogenic section of pedunculopontine nucleus, which have not been confirmed in primates (Takakusaki et al. 2003; Pahapill and Lozano 2000). As for the effects of STN stimulation on the APA, higher-level structures should be considered, with particular reference to pre-motor and supplementary motor areas (SMA). Indeed, in addition to the proposed involvement of the SMA in the control of APA associated with upper limb tasks (Massion et al. 1989), this region was shown to be bilaterally activated prior to the execution of externally cued gait initiation tasks (Yazawa et al. 1997). Moreover, defective activation of SMA was demonstrated in PD during various locomotor tasks (Hanakawa et al. 1999), including gait initiation failure (Vidailhet et al. 1993). Again, increased blood flow in the SMA region was documented during STN stimulation (Limousin et al. 1997; Ceballos-Baumann et al. 1999). Based on the earlier pieces of evidence it might be surmised that positive effects of STN stimulation on the APA associated with the gait onset might involve an influence on the SMA function. Neural substrates for such an ascending action might be the rich connections linking STN and SMA via internal Globus Pallidus and motor thalamic nuclei (e.g. VLo/c, VPLo, Vapc; see Nakano 2000 for a recent review). The finding of a more significant responsiveness of postural and locomotor signs upon attention-demanding operational conditions associated to preparation to move might lead to speculate that, in addition to the "motor" (lateral-dorsal) portion of STN, which through the pallido-thalamo-cortical loops, projects to the pre-central cortices including SMA-proper, the associative "complex" portion of STN is involved as well, which partly shares the same relay stations and projects more anteriorly to the pre-SMA region and to the pre-frontal associative cortex. The integrated firing patterns from the motor, associative (and limbic) portions of the STN are known to shape the pallidal output and, in turn, to influence motor and non-motor functions, including cognitive treatment of sensory input for the guidance of intentional movement (Pesenti et al. 2003). In fact, Malouin et al. 2003 using PET scanning have recently shown specific activation of pre-motor cortical structures, including the pre-SMA region, during mental representation of the gait initiation process.

In conclusion, our data demonstrate substantial influence of STN stimulation on functionally basic motor control mechanisms. In particular, the evidence of more significant responses upon behavioral conditions implying increased attentional demand, as well as the remarkable effects on postural programmes sub-serving feed-forward regulation of the onset of complex multijoint movements, suggest an action on postural subsystems relying on cognitive data processing and internal models of body mechanics.

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