Effects of nigral stimulation on locomotion and postural stability in patients with Parkinson's disease

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The physiopathology of gait and balance disorders in Parkinson's disease patients is still poorly understood. Levodopa treatment and subthalamic nucleus (STN) stimulation improve step length and walking speed, with less effect on postural instability. These disorders have been linked to dysfunction of the descending basal ganglia outputs to brainstem structures. In this study, we evaluated the effects of stimulation of the substantia nigra pars reticulata (SNr), on locomotion and balance in Parkinson's disease patients. Biomechanical parameters and leg muscle activity were recorded during gait initiation in seven selected patients operated for bilateral STN stimulation, out of 204 stimulated patients, with one contact of each electrode located within the SNr. Step length, anteroposterior and vertical velocities of the centre of gravity were studied, with special reference to the subjects' ability to brake the centre of gravity fall before foot-contact, and compared to seven controls. In Parkinson's disease patients, five treatment conditions were tested: (i) no treatment, (ii) levodopa treatment, (iii) STN stimulation, (iv) SNr stimulation and (v) combined levodopa treatment and STN stimulation. The effects of these treatments on motor parkinsonian disability were assessed with the UPDRS III scale, separated into 'axial' (rising from chair, posture, postural stability and gait) and 'distal' scores. Whereas levodopa and/or STN stimulation improved 'axial' and 'distal' motor symptoms, SNr stimulation improved only the 'axial' symptoms. Compared to controls, untreated Parkinson's disease patients showed reduced step length and velocity, and poor braking just prior to foot-contact, with a decrease in both soleus (S) and anterior tibialis (AT) muscle activity. Step length and velocity significantly increased with levodopa treatment alone or in combination with STN stimulation in both natural and fast gait conditions, and with STN stimulation alone in the fast gait condition. Conversely, SNr stimulation had no significant effect on these measures in either condition. In the fast gait condition, braking was improved with STN or SNr stimulation but not with levodopa treatment, with an increase in the stance leg S muscle activity. These results suggest that anteroposterior (length and velocity) and vertical (braking capacity) gait parameters are controlled by two distinct systems within the basal ganglia.
Introduction

The pathophysiology of gait and balance disorders in patients with Parkinson’s disease is not fully understood. Parkinsonian gait disorders consist of reduced walking speed and step length (Blin et al., 1991; Giladi, 2001). Postural instability compromises the ability to maintain balance during everyday tasks and can result in falls, which constitute a major public health problem (Wenning et al., 1999; Bloem et al., 2001; Stolze et al., 2004). Almost 50% of falls occur during walking, in particular during the initiation and termination of gait (Ashley et al., 1977; Masud and Morris, 2001). Gait is a dynamic and periodic process during which loss and recovery of balance alternate. Because two-thirds of human body mass is located two-thirds of body height above the ground, body position would be inherently unstable without a continuously active postural control system (Winter, 1995). Walking can be thought of as being underpinned by two different motor programmes: (i) the adoption of an erect position and its maintenance when performing movements that disturb the centre of gravity (CG) and (ii) the generation of forward motion while stepping, in other words balance and locomotion respectively. During the single support phase of gait initiation, there is a falling phase in the CG, followed by a phase of braking of the CG fall (hereafter referred to as ‘braking’). The CG fall can be arrested by activation of the ankle plantar flexors, prior to foot-contact of the swing limb (‘active mode’), or by the swing limb hitting the ground (‘passive mode’). The active mode is used by normal adults (Welter et al., 2007). This vertical impulse in the CG is altered when normal subjects are unbalanced (Fiolkowski et al., 2002). The passive mode could reflect a disruption of balance control as observed in patients with progressive supranuclear palsy (PSP), a Parkinsonian neurodegenerative disorder characterized by frequent early falls caused by severe postural instability unresponsive to dopaminergic agents (Welter et al., 2007), and in Parkinsonian patients suffering from postural instability (Chastan et al., 2008). Gait and balance disorders appear late in the course of Parkinson’s disease with long-term aggravation and poor responsiveness to levodopa replacement therapy suggesting that they may result from additional non-dopaminergic lesions (Bonnet et al., 1987). In advanced forms of Parkinson’s disease, high frequency stimulation of the subthalamic nucleus (STN) or the internal part of the globus pallidus (GPi), one of the two main outputs of the basal ganglia, has been proposed with good postoperative outcome (Walter and Vitek, 2004; Hamani et al., 2006; Kleiner-Fisman et al., 2006), provided selection criteria are respected (Welter et al., 2002).

Recently, low frequency stimulation of the pedunculopontine nucleus (PPN) region has been shown to improve Parkinsonian gait and balance disorders similarly to high frequency STN stimulation (Stefani et al., 2007) suggesting that these axial symptoms are controlled, at least in part, by this mesencephalic structure. In mammals, two mesencephalic structures involved in gait and postural control have been described: the PPN and the mesencephalic locomotor region (MLR) or cuneiform nucleus (CNF) (Takakusaki et al., 2003). These structures project efferent pathways to the lower brainstem and spinal cord and received afferents inputs from basal ganglia structures (the substantia nigra pars reticulata (SNr), the STN and the GPi), premotor and supplementary motor cortical areas, and limbic system with hypothalamic orexinergic system (Pahapill and Lozano, 2000; Takakusaki et al., 2005). Excitatory projections from the hypothalamic orexinergic system to mesencephalic structures facilitate locomotion. The basal ganglia system receives its main inputs from cortical areas, median nuclei of the thalamus and hippocampus (Obeso et al., 2000). The basal ganglia system is involved in the selection, planning and execution of learned motor programme such as gait initiation and steady-state locomotion in human (Dietz, 1993). Two major descending basal ganglia pathways project GABA inhibitory efferents to the PPN and the MLR (Takakusaki et al., 2005). In animals, modulation of SNr activity, by micro-injections of GABAergic agents, lesions or electrical stimulation, modify both locomotion and postural control (Burbaud et al., 1998; Takakusaki et al., 2003; Henderson et al., 2005). However, to our knowledge, the SNr has never been deliberately examined as a target for axial symptoms in Parkinson’s disease patients (Bejjani et al., 1999; Caire et al., 2006). This paper reports the effects of high frequency SNr stimulation on locomotion and balance control during the gait initiation process, particularly the ability to brake the CG fall during stepping which reflects postural control during gait, in seven Parkinsonian patients operated for bilateral STN stimulation with electrode contacts located within the SNr.

Methods

Patients

Between February 1996 and December 2005, 204 Parkinsonian patients were operated for bilateral STN stimulation at the Pitié-Salpêtrière University Hospital, Paris. Electrodes were implanted in a single operation under local anaesthesia using a target location technique combining intra-operative recordings and stimulation,
obtained from each patient (Yelnik et al., 2007) can be distorted in such a way as to adjust to individual patient's brains. Localisation of the electrodes and their four contacts was determined in 145 patients by superimposing the individual patient's brains. Localisation of the electrodes and their logical level of resolution with accurate 3D alignment. This atlas obtained from each patient (Yelnik et al., 2003). From the sample of 204 patients, 14 patients were retrospectively identified who satisfied the criterion of at least one contact (always the most ventral contact) of each quadripolar electrode located within the SNr (Fig. 1). Three patients had died, two suffered dementia and could not therefore be included in this study and two others were unwilling to participate. Finally, seven patients were included in this study (five men, two women), age was 61.0 ± 7.0 years (mean ± SD), range = 50–68. Mean disease duration was 18.3 ± 4.2 years (13–20) and time since STN stimulation was 43.6 ± 20.1 months (20–72). The daily dose of levodopa equivalent was 421 ± 252 mg/day (100 – 800). Thirteen of the 14 therapeutic contacts were localized within the STN (seven in the right and six in the left STN) and one therapeutic contact was localized within the left Forel's field h2, leading to optimal clinical improvement (Fig. 1). Seven, sex and age matched, control subjects were also included (mean age ± SD: 60.7 ± 7.4 years). The study was supported by the INSERM (RBM: 02–60), and approved by the local Ethics Committee. All subjects gave informed written consent.

**Test procedure**

**Clinical evaluation**

Evaluation of motor disability in the Parkinson's disease patients was performed with the Unified Parkinson's disease Rating Scale part III (UPDRS III) (Fahn et al., 1987). The 'axial' score was defined as the sum of items 27–30 of the UPDRS III (rising from chair, posture, postural stability and gait). The 'distal' score was defined as the difference between the UPDRS III score and the ‘axial’ score without the items 18, 19, 20 and 22 (speech, facial expression, lip tremor and neck rigidity).

The patients were tested in five conditions: (i) ON STN stimulation/OFF drug, using the chronic STN stimulation parameters and after a night without anti-Parkinsonian medication; (ii) ON SNr stimulation/OFF drug, after activation of the DBS stimulator on SNr contacts for at least 1 h (Fig. 1); (iii) OFF stimulation/OFF drug, after deactivation of the DBS stimulator for at least 1 h; (iv) OFF stimulation/ON drug, after the administration of a single suprathereshold dose of levodopa (identical to that used for the preoperative motor assessment, i.e. with a 50 mg more than the usual effective preoperative morning dose); and (v) ON STN stimulation/ON drug, after activation of the DBS stimulator using the chronic STN stimulation parameters with levodopa treatment. The first condition (ON STN stimulation/OFF drug) was performed randomly either before (n = 5) or after (n = 2) the second condition (ON SNr stimulation/OFF drug) to avoid order effects. All five conditions were tested on the same day. STN stimulation parameters were: monopolar cathodal using contact #3 (n = 6), #2 (n = 7) and #1 (n = 1), where #3 was the most dorsal contact; pulse width 60 μs (n = 12) and 90 μs (n = 2); mean stimulation frequency 159 Hz (range: 130–190 Hz); mean stimulation voltage 3.17 ± 0.46 V (range: 2.2–3.7). SNr stimulation was monopolar cathodal using the most ventral contact #0 in all patients (Fig. 1). Pulse width and stimulation frequency were 60 μs and 130 Hz, respectively. SNr stimulation intensity was progressively increased until the occurrence of persistent adverse effects (brachiofacial dystonia (n = 1), diplopia (n = 4), heaviness of eyelids (n = 1), heaviness of lower limbs (n = 1)), and then reduced to 90% of this value. The mean ± SD intensity of SNr stimulation was 2.5 ± 0.68 V (range: 1.4–3.5).

**Gait initiation walking test**

Subjects, barefoot and standing upright and motionless on a force plate, were instructed to commence walking for 5 m following a beep delivered by the experimenter. Two experimental conditions were tested: (i) the ‘natural’ gait condition where subjects walked normally and (ii) the ‘fast’ gait condition where subjects walked as fast as they could, taking large steps. Each subject performed 10 trials in each condition and was allowed to rest between trials.
The ‘natural’ and ‘fast’ gait conditions were assessed in the five stimulation and treatment conditions described above.

**Biomechanical analysis**

Step length (L), peak progression velocity (Vm) of the first step and vertical velocity of the centre of gravity (CG) were measured (Fig. 2) (Brenière and Bril, 1988; Welter *et al.*, 2007). These variables were obtained from a force platform (0.9 × 1.8 m, Advanced Mechanical Technology Inc LG6-4-1, USA) which provided continuous signals proportional to the ground reaction forces (Rx, Ry, Rz in Newtons) and moments (Mx, My, Mz in Newton meters) with respect to the mediolateral (x), anteroposterior (y) and vertical (z) axes of the force plate. The force plate analogue signals were digitized at 500 Hz, CG accelerations and velocities, and centre of foot pressure (CP) displacements were calculated in real time using the Evolution™ physiological acquisition package (V3.5 Notocord SA, Croissy-sur-Seine, France). Offline calculations were performed using custom-written VBA macros after exporting the platform data to an Excel™ workbook.

By dividing Mx by Rz, Ry by the subject’s body mass and (Rz—Body Weight) by the body mass, we obtained respectively the anteroposterior displacement of the CP, the anteroposterior CG velocity and vertical CG acceleration. L was measured from the anteroposterior CP displacement corresponding to the distance between its initial position (t0) and its position at the foot-off (FO2) time of the trailing stance foot (Fig. 2, first trace). The Vm of the CG reached at the end of the first step (Fig. 2, second trace) and the vertical velocity of the CG were also measured (Fig. 2, third trace). In normal adults, the vertical velocity of the CG curve is V shaped and displays negative values during the swing phase, indicating that the CG is falling (the CG fall is represented by V1, the minimum negative vertical velocity

![Fig. 2 Biomechanical parameters and lower limb muscle activity during gait initiation in an individual control subject and a Parkinsonian patient without levodopa treatment or stimulation (OFF stimulation/OFF drug), in natural and fast gait conditions. From top to bottom, curves represent the anteroposterior displacement of the CP allowing the measurement of L, the anteroposterior velocity of the CG with the measure of Vm, the vertical velocity of the CG, activities of anterior tibialis and S muscles of the stance and swing legs. V1 = minimum negative vertical velocity of the CG; V2 = vertical velocity of the CG at foot contact; t0 = first detectable mechanical displacement; FO = foot-off of the swing leg; FC = foot-contact of the swing leg; FO2 = foot-off of the stance leg.](https://academic.oup.com/brain/article-abstract/132/1/172/288883)
of the CG, i.e. the trough of the V). Before foot-contact, there is a reversal of the CG fall and the vertical velocity of the CG increases prior to foot-contact. At foot-contact, the vertical velocity of the CG (V2) is then higher than the minimum vertical velocity of the CG during the single support phase (V1), indicating that there is an active braking of the CG fall before foot-contact. The increase in the CG vertical velocity prior to foot-contact \((V1-V2)/V1\times100\) represents the subject’s ‘braking capacity’.

**EMG recordings**

The activity of both soleus (S) and anterior tibialis (AT) muscles was simultaneously recorded bilaterally at a sampling rate of 5 kHz using bipolar surface electrodes. The EMG signals were amplified, band-pass filtered from 50 Hz to 5 kHz and rectified (Fig. 2, four lower traces). Muscle activity was quantified by dividing the surface area of the EMG amplitude profile of each period by its duration. The integrated EMG signal was quantified over three periods of gait initiation: (i) during the anticipatory postural adjustment phase, between t0 and the foot-off; (ii) during the CG fall, between the foot-off and the minimum negative vertical velocity of the CG (V1) and (iii) during the braking of the CG fall, between the minimum negative vertical velocity of the CG (V1) and foot-contact (Fig. 2).

**Statistical analysis**

The 10 trial means and standard deviations of ‘natural’ and ‘fast’ gait conditions were calculated for each biomechanical parameter. Similarly, the mean and standard deviations of the clinical measures were calculated for each stimulation condition. The effects of levodopa treatment, STN and SNr stimulation on Parkinsonian motor symptoms and biomechanical parameters of gait were evaluated by comparing the OFF stimulation/OFF drug condition with the other four stimulation conditions (ON STN stimulation/OFF drug, ON SNr stimulation/OFF drug, OFF stimulation/ON drug and ON STN stimulation/ON drug), by means of the Wilcoxon matched pairs test. The differential effects of STN and SNr stimulation on Parkinsonian motor symptoms and gait parameters were assessed by means of the Wilcoxon matched pairs test (ON STN stimulation/OFF drug versus ON SNr stimulation/OFF drug). The relationship between Parkinsonian motor symptoms and gait parameters was measured using the Spearman rank-correlation test. The accepted significance level was \(P<0.05\).

**Results**

**Effects of levodopa treatment, subthalamic or nigral stimulation on Parkinsonian motor disability**

In comparison to the OFF stimulation/OFF drug condition, the Parkinsonian motor disability score (UPDRS III) improved significantly by 67% with levodopa treatment \((P=0.03)\), 74% with STN stimulation \((P=0.02)\) and 85% with combined STN stimulation and levodopa administration \((P=0.03)\) with no significant change with SNr stimulation (Fig. 3A).

**Fig. 3** Effects of levodopa treatment and STN or SNr stimulation on Parkinsonian motor disability (UPDRS III- A), axial (B), gait and postural stability scores (C) in seven Parkinsonian patients. Parkinson’s disease patients were evaluated in five conditions: OFF = OFF stimulation/OFF drug; L-DOPA = with levodopa treatment; STN = with subthalamic stimulation, SNr = with nigral stimulation, ON = with combined levodopa treatment and STN stimulation. A and B: each symbol represents one subject. \(*P<0.05\) compared with the condition OFF stimulation/OFF drug.
In comparison to the OFF stimulation/OFF drug condition, axial symptoms improved significantly with levodopa treatment (−67%, \( P = 0.03 \)), STN (−49%, \( P = 0.03 \)) or SNr (−44%, \( P = 0.04 \)) stimulation, and with combined STN stimulation and levodopa administration (−78%, \( P = 0.03 \)) (Fig. 3B).

In comparison to the OFF stimulation/OFF drug condition, the gait subscore improved significantly by 81% with levodopa treatment alone or in combination with STN stimulation (\( P = 0.01 \)), and by 50% with STN or SNr stimulation (\( P = 0.02 \), Fig. 3C left). In comparison to the OFF stimulation/OFF drug condition, the postural stability subscore improved significantly with levodopa treatment alone or in combination with STN stimulation (−80%, \( P = 0.03 \)), STN (−50%, \( P = 0.05 \)) or SNr (−60%, \( P = 0.02 \)) stimulation alone (Fig. 3C right).

The ‘distal’ score improved significantly by 68% with levodopa treatment (\( P = 0.03 \)), 77% with STN stimulation (\( P = 0.02 \)), and 86% with combined STN stimulation and levodopa administration (\( P = 0.02 \)). With SNr stimulation, the ‘distal’ score showed no significant change (−15%, not shown).

In summary, our results show that bilateral SNr stimulation significantly improved only axial Parkinsonian motor symptoms whereas bilateral STN stimulation significantly improved global, distal and, to a lesser degree, axial symptoms (Fig. 3, Table 1).

### Biomechanical parameters of gait initiation

In controls, the length and velocity of the first step were 33% and 40% greater in the fast compared to the natural gait condition (\( P < 0.001 \), Figs 2–4A). The minimum negative vertical velocity of the CG (V1), which represents the CG fall and the CG vertical velocity at foot-contact (V2) were significantly lower (\( P < 0.01 \), Fig. 2), and the braking capacity was unchanged between the two conditions (−7%, \( P = 0.29 \), Figs 2–4B). During initiation of gait, the pattern of lower limb muscle activity was similar in both natural and fast gait conditions (Fig. 2). The AT muscle activity of both legs significantly increased at the point of the first detectable movement (t0) and persisted during the whole anticipatory postural adjustments phase, and decreased during the CG fall and the braking phase (\( P < 0.005 \)). The swing leg AT muscle activity increased just before foot-contact. The \( S \) muscle activity of the stance leg was minimal during the anticipatory postural adjustments, increased significantly during the CG fall and increased again during the braking phase (\( P < 0.0001 \)). The \( S \) muscle activity of the swing leg increased significantly before foot-off, then decreased during CG fall and the braking phase but increased just prior to foot-contact (Fig. 2).

In Parkinsonian patients (OFF stimulation/OFF drug condition), the length and velocity of the first step were significantly lower in the natural gait condition, compared to controls (\( P < 0.04 \), Figs 2–4A left). In four patients, step length was <40cm and consequently no CG fall occurred implying that braking before foot-contact was unnecessary. In the fast compared to the natural gait condition, length and velocity of the first step significantly increased (+42% and +45%, respectively, \( P < 0.005 \), Figs 2–4A right), whereas the CG fall (V1) and the vertical velocity at foot-contact (V2) significantly decreased (\( P < 0.005 \), Fig. 2). Braking capacity was unchanged (−25%, \( P = 0.38 \)) and was significantly lower than controls (\( P < 0.02 \), Figs 2–4B right). Compared to controls, the pattern of lower limb EMG activity was altered in Parkinsonian patients in the OFF stimulation/OFF drug condition, both in the natural and fast gait conditions (Fig. 2). In the stance leg, no significant change in the AT activity was observed during the whole gait initiation process. The activity of the stance leg \( S \) muscle was significantly lower during the CG fall and braking phases. In the swing leg, the AT muscle was less active during the anticipatory postural adjustment phase, before foot-off, with no significant change during the CG fall and braking phases. In the swing leg \( S \) muscle, activity was significantly lower, with a relative preservation of the muscle activity pattern (Fig. 2).

### Effects of levodopa treatment, subthalamic or nigral stimulation on biomechanical parameters of gait in Parkinsonian patients

#### Step length

In the ‘natural’ gait condition, compared to the OFF stimulation/OFF drug condition, \( L \) was 32% higher under levodopa treatment, and 41% higher with combined STN stimulation and levodopa treatment (\( P = 0.02 \) in both cases). No significant change in step length was noted with either STN or SNr stimulation (Fig. 4A left).

In the ‘fast’ gait condition compared to the ‘natural’ gait condition, step length was significantly higher in all stimulation and treatment conditions (Fig. 4A). In comparison to the OFF stimulation/OFF drug condition, step length was higher by 12% under levodopa treatment, 11% with STN stimulation, and 19% with the combination of STN stimulation and levodopa treatment (\( P = 0.02 \) in all cases, Figs 4A, right–5). No significant change in the step length was observed with SNr stimulation.

#### Peak progression velocity

In the ‘natural’ gait condition, in comparison to the OFF stimulation/OFF drug condition, the \( V_m \) was 33% greater under levodopa treatment (\( P = 0.03 \)), and 40% greater with combined STN stimulation
and levodopa treatment ($P=0.02$) (Fig. 4A left lower graph). No significant change in $V_m$ was observed with either STN or SNr stimulation alone.

In the ‘fast’ compared to the ‘natural’ gait condition, $V_m$ was significantly greater in all stimulation and treatment conditions (Fig. 4A). In comparison to the OFF stimulation/OFF drug condition, $V_m$ was 14% greater under levodopa treatment ($P=0.03$), 12% with STN stimulation ($P=0.03$), and 21% with combined STN stimulation and levodopa treatment ($P=0.02$) (Fig. 4A right lower graph–5). There was no significant change in the maximum peak velocity with SNr stimulation alone.

CG fall and braking capacity

In the natural gait condition, in comparison to the OFF stimulation/OFF drug condition, the minimum negative vertical velocity of the CG ($V_1$) was significantly lower under levodopa treatment, STN stimulation alone or in combination with levodopa treatment ($P<0.005$). As four patients had step lengths $<40$ cm in all natural gait stimulation and treatment conditions (Fig. 5), with in consequence only a slight CG fall, the braking capacity in all stimulation and treatment conditions could therefore only be measured in the ‘fast’ gait condition.

In the ‘fast’ gait condition compared to the OFF stimulation/OFF drug condition, no significant change in the CG fall ($V_1$) and the vertical velocity of the CG at foot-contact ($V_2$) was observed in any of the treatment and stimulation conditions (Fig. 5). STN or SNr stimulation significantly improved the degree of braking in comparison to the OFF stimulation/OFF drug condition ($V_2-V_1$, +71% and +99%, respectively) (Fig. 4b upper right graph) and the braking capacity (+41% and +86%, respectively) (Figs 4b lower right graph–5), whereas levodopa treatment with or without STN stimulation induced no significant change in braking capacity.

Lower limb EMG activity

In the stance leg, compared to the OFF stimulation/OFF drug condition, the TA muscle activity did not change significantly with levodopa treatment, STN or SNr stimulation (Figs 5 and 6A left). The S muscle activity however was significantly higher during STN stimulation within both the CG fall ($FO_1-V_1$) and braking ($V_1-V_2$) phases, and increased with SNr stimulation during the braking phase, in particular in patients showing improved braking capacity (Figs 5–6A right). In the swing leg, comparison with the OFF stimulation/OFF drug condition, showed no significant change in either TA and S muscle activity with either levodopa treatment, STN or SNr stimulation (Fig. 6B).

In summary, SNr stimulation improved only the vertical biomechanical measure of braking capacity with an increase in the S activity of the stance leg during the braking phase whereas STN stimulation improved both the anteroposterior and vertical biomechanical parameters of gait initiation, with an increase in

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**Fig. 4** Effects of levodopa treatment and STN or SNr stimulation on length and velocity of the first step (A) and braking capacity (B) in seven Parkinsonian patients, in both natural and fast gait conditions. (C) controls. Parkinson’s disease patients were evaluated in five conditions: OFF = OFF stimulation/OFF drug; L-DOPA = with levodopa treatment; STN = with subthalamic stimulation; SNr = with nigral stimulation; ON = with combined levodopa treatment and STN stimulation. Each symbol represents one subject. “$P<0.05$ when compared OFF stimulation/OFF drug PD patients with controls.” $P<0.05$ compared with the condition OFF stimulation/OFF drug.
the S activity of the stance leg during the execution of the first step (Table 1).

**Relationship between motor Parkinsonian symptoms and biomechanical gait parameters**

The ‘axial’ score was significantly negatively correlated with $L$ ($r = -0.7 \ P < 0.0001$ and $r = -0.6 \ P = 0.0002$ respectively), $V_m$ ($r = -0.4 \ P = 0.001$ and $r = -0.5 \ P = 0.001$ respectively) and degree of braking ($V_2 - V_1$) ($r = -0.6 \ P = 0.001$ and $r = -0.3 \ P = 0.04$ respectively) in both the ‘natural’ and ‘fast’ gait conditions. No significant correlation was found between the ‘distal’ score and either the length, $V_m$ of the first step or the degree of braking.

**Discussion**

This study showed that, in Parkinson’s disease patients, bilateral STN stimulation improves axial Parkinsonian motor symptoms (gait and balance disorders) and braking capacity of the CG fall but has no effect on distal Parkinsonian motor symptoms (segmental akinesia, rigidity and tremor) and anteroposterior biomechanical parameters of gait (length and velocity of the first step). Conversely, STN stimulation improves both distal and axial Parkinsonian motor symptoms and both anteroposterior and vertical biomechanical parameters of gait (Table 1).

These results are robust as the group of Parkinson’s disease patients was homogeneous and carefully selected (Welter et al., 2002), using identical neurosurgical procedures. All Parkinson’s disease patients were evaluated by the same experimenter,
under the same conditions, with postoperative OFF stimulation/ OFF drug Parkinsonian motor scores similar to those obtained before surgery without levodopa treatment (OFF drug, Fig. 3). The location of the electrode contacts was determined using a reliable, validated method (Yelnik et al., 2003) and 13 STN and all SNr (n = 14) contacts were similarly placed (Fig. 1B). One STN therapeutic contact was located in Forel’s field H2, stimulation of this structure has been demonstrated to have a similar clinical effect to STN stimulation, however (Vergani et al., 2007). In the substantia nigra, stimulation was confined to the pars reticulata (Fig. 1B). Lastly, it is unlikely that current spread from STN stimulation could have influenced the SNr or vice versa as (i) the STN contacts used in our patients were separated from those in the STN by at least 4 mm in 13 of the 14 electrodes of our seven Parkinson’s disease patients (6 mm for six contacts, 4 mm for seven contacts), and only by 2 mm in one electrode and (ii) it has been previously shown that a 3 V monopolar stimulation can activate axonal elements within a radius of 2.5 mm from the centre of the electrode contact (Wu et al., 2001) with a maximum of 4 mm when the electrode is localized within the STN, taking into account tissue electrical properties (McIntyre et al., 2004). For all these reasons, we consider the results of this study to be reliable despite the small patient sample (n = 7). However, this number could not be increased despite the analysis of the electrode positions of 204 patients implanted at our centre, in which only a small number of patients could be found with implanted bilateral electrode contacts selectively located within the SNr.

Fig. 6 Effects of levodopa treatment and STN or SNr stimulation on lower limb muscle activity in seven Parkinsonian patients. The same symbol for each subject as in Figs 3 and 4.
Effects of subthalamic high frequency stimulation and levodopa treatment

It has been shown previously that Parkinsonian motor distal and axial symptoms are both improved under levodopa replacement therapy or STN stimulation (Limousin et al., 1998; Bejani et al., 2000b; Krack et al., 2003; Schupbach et al., 2005). Similarly, length and velocity of the first step (anteroposterior gait initiation parameters) increase with these two treatments (Blin et al., 1991; Azulay et al., 1996; Allert et al., 2001; Faist et al., 2001; Stolze et al., 2001; Bastian et al., 2003) (Fig. 3A), with an improvement in the asymmetry of gait, single and double support times and progression of the CP (Allert et al., 2001). This suggests that reduced length and velocity of the first step result mainly from the decreased dopaminergic transmission characteristic of the disease, in line with data obtained in mice with MPTP-induced degeneration of nigro-striatal dopamine transmission (Fernagut et al., 2002). Postural control is altered in Parkinson’s disease patients with an increase in postural oscillations during quiet standing (Mitchell et al., 1995; Rocchi et al., 2004). Subthalamic stimulation has been shown to improve postural control in a static position (Rocchi et al., 2004; Colnat-Coulbois et al., 2005) and during gait initiation, with a reduction in the imbalance phase and a larger anteroposterior and mediolateral displacement of the CP during anticipatory postural adjustments (Crenna et al., 2006). In this study, the braking capacity of the CG fall was not significantly altered by levodopa treatment, while STN stimulation improved it (Fig. 4B). This suggests that this gait initiation process, i.e. the braking capacity, which could reflect postural control during gait (Welter et al., 2007), is not directly controlled by brain dopaminergic systems but is dependent upon basal ganglia activity, in particular that of the STN. The fact that this mechanism is severely altered in PSP patients (Welter et al., 2007) who showed severe degeneration of STN neurons (Hauw et al., 1994; Litvan et al., 1996) is in line with this hypothesis.

Effects of SNr high frequency stimulation

High frequency stimulation of the SNr dramatically improved axial, but not distal, Parkinsonian motor symptoms (Fig. 3), with an increase in braking capacity (Figs 3A–4). These SNr stimulation effects are in line with observations of severe axial postural anomalies induced by injections of GABAergic agents into the SNr of normal primates (Burbaud et al., 1998) and reversal of body orientation changes in primates rendered Parkinsonian by SNr lesions, without improvement of the bradykinesia on the centrolateral side (Henderson et al., 2005). As in our study performed in humans, these data suggest that in primates the SNr is primarily involved in postural control. However, injections of GABA agonists into the SNr of monkeys rendered hemi-Parkinsonian show different results depending on the injection site (Wichmann et al., 2001). Centrolateral SNr injection was found to improve both akinesia and bradykinesia, whereas medial SNr injections induced strong behavioural activation, turning and dystonia-like neck and body postures with no effect on limb mobility. In our patients, stimulation was confined to the medial SNr (Fig. 1B), a result which is in agreement with the effects of injections of GABA antagonists in experimental animals. SNr stimulation increased braking capacity with no significant effect on length and velocity of the first step suggesting that SNr controls, at least partly, the braking mechanism, which is thought to reflect the control of balance during gait (Welter et al., 2007). This increase in the capacity to brake the CG fall could result from an increase in the activity of the stance leg S muscle as observed in our patients (Fig. 6A) with an increase in the CG vertical impulse prior to foot landing (Brenière and Bril, 1988). This is in agreement with modulations of both muscle tone inhibitory and locomotion executing systems induced by high frequency (100 Hz) electrical stimulation of the SNr in primates (Takakusaki et al., 2003).

Subthalamic versus nigral high frequency stimulation

High frequency STN stimulation improved both distal and axial mobility whereas SNr stimulation improved only axial motor symptoms. This suggests that the SNr output participates in axial, but not distal, motor control, whereas the STN is involved in both. SNr efferents ascend to the thalamus, but also descend to the brainstem, in particular to the pontomesencephalic area which is known to be involved in locomotion and postural control (Takakusaki et al., 2003). According to the classic basal ganglia functional model, the STN nucleus projects excitatory inputs to both the SNr and the internal segment of the GPi, the two main basal ganglia outputs (Alexander et al., 1990). Previous studies have shown that GPi stimulation improves Parkinsonian motor disability (Krack et al., 1998; Volkmann et al., 2001; Anderson et al., 2005), with less improvement in axial symptoms (Krack et al., 1998; Allert et al., 2001; Rodriguez-Oroz et al., 2005), suggesting that GPi stimulation preferentially improves motor Parkinsonian distal symptoms. From a neurophysiological point of view, we observed a similar dichotomy with an improvement of both anteroposterior and vertical gait initiation parameters with STN stimulation whereas SNr stimulation only improves vertical measures, i.e. the CG fall braking capacity. Unfortunately it was not possible to examine Parkinson’s disease patients with bilateral pallidal stimulation in our centre. Pallidal stimulation has been reported to improve step length and velocity of the first step with a decrease in double support time and an increase in single support time (Krystkowiak et al., 2001; Defebvre et al., 2002), although with a smaller effect than with STN stimulation (Allert et al., 2001). Pallidal stimulation had less effect on postural control with no significant change in CP displacements during anticipatory postural adjustments (Defebvre et al., 2002) and a larger variability in CP displacement during quiet standing (Rocchi et al., 2004). This suggests that STN stimulation induces a decrease in both distal and axial Parkinsonian motor symptoms and both anteroposterior and vertical parameters of gait initiation by its effects on both GPi and SNr neuronal activity (Hashimoto et al., 2003; Maltête et al., 2007), whereas stimulation of the SNr only modulates SNr activity with a consequent decrease in axial motor symptoms and an improvement in vertical gait parameters.
Both SNR and STN project ascending efferents, via the GPi and the SNr for the STN, to the thalamus which projects inhibitory efferents to cortical areas (Alexander et al., 1990). Improvement in axial motor symptoms and vertical gait parameters could thus result from changes in cortical activity. Using functional imaging and neurophysiological approaches, it has been shown that STN stimulation normalizes cortical activity related to the control of movement (Devo et al., 2004), in particular in the supplementary motor area (Grafton et al., 2006). Recently, a relationship between improvement in freezing of gait and metabolic activity of the parietal, occipital and temporal sensory association cortices has been reported (Lyoo et al., 2007).

Role of the mesopontine tegmental structures in the braking mechanism

In addition to their ascending efferent pathways, both STN and SNr project descending efferents to the mesopontine tegmental area, with GABAergic inhibitory inputs to the PPN and the CNF for the SNr, and glutamatergic excitatory inputs to the PPN for the STN (Obeso et al., 2000). In animals, these two structures, located in mesopontine tegmentum, have been shown to be widely implicated in the control of postural muscle tone and locomotion (Prentice and Drew, 2001; Takakusaki et al., 2003). In decerebrate cats, activation of the CNF (which is part of the so-called midbrain locomotion region or MLR) increases muscle tone and induces locomotion when animals are placed on a moving treadmill (Takakusaki et al., 2003). Activation of the ventral PPN is required to initiate locomotion (Garcia-Rill, 1991) and suppresses postural muscle tone (Takakusaki et al., 2003). In Parkinson’s disease, it is thought that the GABAergic inhibitory inputs are overactive with an excessive inhibition of the MLR with gait failure and of the PPN with an increase in the level of muscle tone. High frequency stimulation of the SNr may reduce this excess inhibition by inducing a reduction of the SNr neuronal activity, as reported in the STN with during STN stimulation (Welter et al., 2004), resulting in an increase in the braking mechanism and decrease in gait and balance disorders in Parkinson’s disease patients (this study). The fact that a dramatic alteration of the braking mechanism has been observed in PSP patients (Welter et al., 2007), who show a loss of PPN neurons (Hirsch et al., 1987), and in Parkinson’s disease patients with levodopa unresponsive postural instability and mesencephalic area atrophy is in line with this hypothesis. Recently, low frequency PPN stimulation (which is thought to activate PPN neurons) has been reported to improve gait impairement and postural instability in Parkinson’s disease patients (Stefani et al., 2007), with modulation of spinal excitability (Pierantozzi et al., 2008). In contrast to high frequency SNr stimulation, low frequency PPN stimulation also improves non-axial Parkinsonian motor symptoms, presumably as a result of the ascending PPN projections to the STN and the GPi (Pahapill and Lozano, 2000).

Conclusion

SNr stimulation improves clinical axial symptoms but not distal ones. We propose that the SNr and GPi basal ganglia outputs map separately onto the downstream motor systems controlling these two aspects of PD symptomatology. Whereas SNr output principally influences axial movement (but not distal), the GPi output influences, at least, distal movement, with the STN influencing both because of its projections to the two output nuclei.

Vertical biomechanical analysis obtained using a force platform is a new tool for the study of postural control during gait. Our stimulation results imply that the SNr output is involved in the braking mechanism probably as a result of its projection to the PPN. Since the SNr is located just underneath the STN and because during the normal surgical procedure for STN electrode implantation, the SNr is usually targeted for electrophysiological recordings, the SNr could be envisaged as a complementary therapeutics target in Parkinson’s disease patients selected for surgery for the treatment of gait and balance disorders. However, further investigation will be required to determine the effects of combined STN and SNr stimulation in Parkinson’s disease patients with axial motor impairment.

References


