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# Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up

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**Deep brain stimulation (DBS) is associated with significant improvement of motor complications in patients with severe Parkinson's disease after some 6–12 months of treatment. Long-term results in a large number of patients have been reported only from a single study centre. We report 69 Parkinson's disease patients treated with bilateral DBS of the subthalamic nucleus (STN, *n* = 49) or globus pallidus internus (GPi, *n* = 20) included in a multicentre study. Patients were assessed preoperatively and at 1 year and 3–4 years after surgery. The primary outcome measure was the change in the 'off' medication score of the Unified Parkinson's Disease Rating Scale motor part (UPDRS-III) at 3–4 years. Stimulation of the STN or GPi induced a significant improvement (50 and 39%; *P* < 0.0001) of the 'off' medication UPDRS-III score at 3–4 years with respect to baseline. Stimulation improved cardinal features and activities of daily living (ADL) (*P* < 0.0001 and *P* < 0.02 for STN and GPi, respectively) and prolonged the 'on' time spent with good mobility without dyskinesias (*P* < 0.00001). Daily dosage of levodopa was significantly reduced (35%) in the STN-treated group only (*P* < 0.001). Comparison of the improvement induced by stimulation at 1 year with 3–4 years showed a significant worsening in the 'on' medication motor states of the UPDRS-III, ADL and gait in both STN and GPi groups, and speech and postural stability in the STN-treated group. Adverse events (AEs) included cognitive decline, speech difficulty, instability, gait disorders and depression. These were more common in patients treated with DBS of the STN. No patient abandoned treatment as a result of these side effects. This experience, which represents the first multicentre study assessing the long-term efficacy of either STN or GPi stimulation, shows a significant and substantial clinically important therapeutic benefit for at least 3–4 years in a large cohort of patients with severe Parkinson's disease.**

**Keywords**: deep brain stimulation; globus pallidus pars interna; long-term effects; Parkinson's disease; subthalamic nucleus

**Abbreviations**: ADL = activities of daily living; AEs = adverse events; DBS = deep brain stimulation; GPi = globus pallidus pars interna; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

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## Introduction

The management of Parkinson's disease is mainly pharmacological. Levodopa and dopamine agonists are able to provide adequate symptomatic control in the first 5–10 years of therapy. However, long-term evolution is marred in the majority of patients by complications, such as fluctuations in the motor state (the 'wearing-off' and 'on–off' phenomena) and dyskinesias (Marsden and Parkes, 1976; Schrag and Quinn, 2000). In recent years, surgery has been revitalized for the treatment of patients with uncontrollable motor complications. Experimental data in animal models of Parkinson's disease have shown that neuronal activity in the subthalamic nucleus (STN) and globus pallidus pars interna (GPi) is abnormally exaggerated in the parkinsonian state (Mitchell *et al.*, 1989; DeLong, 1990; Bergman *et al.*, 1994; Vila *et al.*, 1997) and lesion or blockade of these nuclei is associated with marked amelioration of parkinsonism (Bergman *et al.*, 1990; Aziz *et al.*, 1991; Guridi *et al.*, 1996; Lonser *et al.*, 1999). The aim of surgery is mainly to decrease the pathological influences of abnormal neuronal drive from the STN and GPi that characterize the parkinsonian state. Deep brain stimulation (DBS) mimics the effect of lesions (thalamotomy, pallidotomy, etc.) with less risk of permanent neurological deficits (Benabid *et al.*, 1987; Montgomery *et al.*, 2000; Schuurman *et al.*, 2000). Several studies have shown a substantial beneficial effect of DBS of the STN or GPi in advanced Parkinson's disease 12–24 months post-operatively (Ghika *et al.*, 1998; Limousin *et al.*, 1998; Rodriguez-Oroz *et al.*, 2000; Durif *et al.*, 2002; Romito *et al.*, 2002; Vingerhoets *et al.*, 2002; Herzog *et al.*, 2003; Kleiner-Fisman *et al.*, 2003; Pahwa *et al.*, 2003; Volkmann *et al.*, 2004). DBS is currently applied worldwide and the benefit to risk ratio of the therapy is under scrutiny. A crucial question in this regard is whether or not the generally satisfactory response reported in early short-term studies is sustained after prolonged follow-up. Recently, the Grenoble group who pioneered this technique (Benabid *et al.*, 1987; Limousin *et al.*, 1995) reported the efficacy of STN DBS in 42 patients after a follow-up of 5 years (Krack *et al.*, 2003). They found that DBS had a persistent anti-parkinsonian effect and reduced levodopa-induced dyskinesias. Similar results have been reported in a smaller number of patients by a few other groups (Kleiner-Fisman *et al.*, 2003; Rodriguez-Oroz *et al.*, 2004).

We previously described the results of a large multi-institutional study involving a double-blind evaluation at 3 months and open evaluation at 6 months (Deep Brain Stimulation for Parkinson's Disease Study Group, 2001). A significant effect of stimulation of either the STN or GPi was found in both the blind and open evaluations. We now report the 3–4 year post-operative follow-up of a large cohort of patients included in the initial study.

## Methods

### Patients

The aim of the present study was to assess the efficacy of bilateral DBS in a large group of patients followed for a minimum of 3 years and <5 years. An intention to treat analysis was not applied. Eight centres (Appendix 1) participated in this extension of a trial originally conducted by 18 centres designed to blindly assess the effect of stimulation at 3 months post-operatively (Deep Brain Stimulation for Parkinson's Disease Study Group, 2001). Ten of the original centres that had recruited 54 patients altogether for the initial study were not included in this follow-up analysis. In no instance was a centre excluded because of the ongoing results. In fact, such analysis has never been undertaken. Nine centres were excluded owing to recruiting a small number of patients ($n < 8$) and another was excluded because of unavailability of the principal investigator and his team.

The characteristics of the patients are summarized in Table 1. The institutional review board of each participating centre approved the follow-up protocol and all patients gave written informed consent to the >3 years evaluation. Electrodes were implanted bilaterally

**Table 1** Demographic characteristics of patients included in the study

| | STN ($n$ = 49) | GPi ($n$ = 20) |
|---|---|---|
| Gender | 24 F/25 M | 7 F/13 M |
| Mean age at implant (years) | 59.8 ± 9.8 (38–75) | 55.8 ± 9.4 (43–70) |
| Mean duration of follow-up (years) | 3.8 ± 0.6 (2.8–5.3) | 3.9 ± 0.7 (3.1–5.2) |
| Mean duration of disease since onset | 15.4 ± 6.3 (6.2–28.4) | 15.4 ± 6.2 (7–32.4) |
| Mean duration of disease since definite diagnosis | 14.1 ± 5.9 (5.7–26.8) | 14.4 ± 5.7 (7–26.4) |
| UPDRS-II | | |
| Off medication | 29.7 ± 8.0 (12.5–44) | 26.8 ± 8.9 (12–43.5) |
| On medication | 10.6 ± 6.7 (0–26) | 12.0 ± 7.2 (0.5–25.5) |
| UPDRS-III | | |
| Off medication | 56.7 ± 15.7 (29.5–85.5) | 51.7 ± 13.6 (24.5–84.5) |
| On medication | 22.8 ± 10.4 (6–43.5) | 18.6 ± 10.3 (6–45) |
| Hoehn and Yahr (off medication) | 4.3 ± 0.8 (2–5) | 4.0 ± 0.8 (3–5) |
| Dyskinesias | | |
| Off dystonia | 0.92 ± 1.10 (0–4) | 0.70 ± 1.15 (0–3) |
| On dyskinesia | 1.95 ± 1.07 (0–4) | 2.83 ± 1.18 (0–4) |
| Equivalent daily dose of levodopa (mg) | 1336 ± 619 (303–3375) | 1074 ± 462 (375–2150) |

Data are presented as mean ± SD. Values in parentheses are range.

under local anaesthesia as described previously (Deep Brain Stimulation for Parkinson's Disease Study Group, 2001). The surgical target (either STN or GPi) was not randomized but decided by each team according to their best clinical judgement at the time of recruitment. As a result, the severity of levodopa-induced dyskinesias was greater in the GPi group than in the STN group as at the time it was generally assumed that surgery of the STN had a higher risk of inducing dyskinesias. The first patient included in the study was operated in January 1996 and the last one in July 1998.

## Study protocol

Evaluations were performed in open fashion by neurologists specialized in movement disorders. The first follow-up evaluation was conducted in February 2000 and the last one in April 2002. Mean ± standard deviation (median) follow-up for the STN and GPi groups were 3.8 ± 0.6 (3.93) and 3.9 ± 0.7 (4.02) years, respectively. Assessments were conducted preoperatively in the poor mobility ('off' medication) and good mobility ('on' medication) states. The 'off' and 'on' pharmacological states were defined, respectively, as the motor scores after 12 h (unless intolerable for particular patients) without medication and the maximum improvement following a dose of levodopa equal to 150% of the usual first morning dose. Patients who had stopped taking levodopa after surgery were given the same dose as preoperatively. Post-operative evaluations were carried out sequentially in the four possible conditions: (i) 'off' medication without stimulation; (ii) 'off' medication with stimulation; (iii) 'on' medication without stimulation; (iv) 'on' medication with stimulation. Off and on stimulation conditions were evaluated 60–120 and 30 min after turning off and on the stimulator, respectively. Evaluations included the Unified Parkinson's Disease Rating Scale (UPDRS) parts II [activities of daily living (ADL); obtained by history] and III (motor) and a dyskinesia scale (Langston *et al.*, 1992; Goetz *et al.*, 1994) that scores the involuntary movements induced by medication ('on' dyskinesias) from 0 (no dyskinesias) to 4 (severe and continuous, highly disabling dyskinesias). Dystonic postures occurring during 'off' medication periods were evaluated separately with the same rating scale.

The global efficacy of therapy was judged by investigators and patients using the Global Assessment scale that scores impairment as follows: 0 = no functional disability, 1 = mild disability (1–24%); 2 = moderate disability (25–49%); 3 = marked disability (50–74%); 4 = severe disability (75–100%). Patients were asked to complete a home diary documenting their motor status at 30-min intervals during two consecutive days prior to each visit. They were instructed to distinguish 'off' (poor mobility), 'on' (good mobility) and 'on' with dyskinesias (good mobility accompanied by involuntary movements). Daily consumption of dopaminergic drugs was calculated as follows: 100 mg of standard levodopa = 130 mg of controlled-released levodopa = 10 mg bromocriptine = 1 mg pergolide = 1 mg lisuride = 1.5 mg pramipexole = 5 mg ropinirole (Reichmann *et al.*, 2003).

The primary outcome measure was the difference in the motor UPDRS (part III) scores in the 'off' medication state between baseline and last post-operative follow-up on stimulation (minimum 3 years). Secondary measurements were the changes induced by stimulation with respect to baseline in the number of daily hours in the 'on' state without dyskinesias (evaluated through 'on–off' diaries) and the effect of stimulation compared with baseline on the following clinical measurements: (i) motor UPDRS in 'on'; (ii) cardinal motor features of Parkinson's disease assessed from the following items of the UPDRS-III: tremor (items 20 and 21), akinesia (23–26), rigidity (22), gait (29), speech (18) and postural stability (28) in the 'off' and 'on' medication states; (iii) ADL (UPDRS-II) in the 'off' and 'on' medication states; (iv) dyskinesia score in the 'off' and 'on' medication states; (v) global efficacy of the therapy by investigators and patients; (vi) comparison of the effect of stimulation on the primary and secondary measurements evaluated at 1 and 3–4 years post-operatively.

Investigators recorded adverse events (AEs) on a preestablished questionnaire in the study protocol. All new medical manifestations or aggravation of prior signs were recorded as AEs. Complications directly associated with the surgical procedure were reported previously (Deep Brain Stimulation for Parkinson's Disease Study Group, 2001). The part I of the UPDRS scale was a routine component of the protocol, thus allowing evaluation of intellectual impairment, thought disorders, depression and motivations/initiative. The severity of AEs was classified by each investigator in accordance with the following protocol definitions: 'mild', when easily tolerated, not interfering or minimally interfering with daily functioning and not requiring treatment; 'moderate', when causing some interference with daily functioning or requiring specific treatment; 'severe' when incapacitating, necessitating urgent treatment or requiring hospitalization, was life threatening, needed surgical intervention or caused death. They distinguished between transient and persistent AEs, and as related to stimulation, drugs, disease progression, concomitant diseases or unknown. Only persistent AE are analysed in this report.

Data were assessed by an *ad hoc* committee (Appendix 2) independent of the clinical investigators and the sponsor. A comprehensive study examining the factors associated with the AEs encountered in this series and hardware-related problems will follow the present paper.

## Statistics

The Wilcoxon rank sum test was applied for comparison between the mean scores preoperatively and at the last assessment and for UPDRS-II and III, cardinal features subscores and dyskinesia scores at the first and third years post-operatively. Pure discrete counting variables were compared using $\chi^2$-tests. Level of significance was 5% taking into account the need for Bonferroni correction in case of multiple testing. However, the statistical assessment did not address one global answer of significance by multiple variables. Thus, it was considered that applying the Bonferroni correction to the analysis was not needed. All *P*-values reported are two-sided. Descriptive statistics *N*, quartiles, mean and standard deviation or frequencies where appropriate were reported. The analysis was performed using SAS release 8.02.

## Role of the funding source

The sponsor (Medtronic Europe) and the participating centres designed and approved the protocol. Medtronic monitored the study and the data were entered into a validated database. A statistician employed by the company performed the statistical analysis based on specific requests of the investigators. Final data were made available to the authors who independent of the sponsor assessed the data analysis as well as the interpretation and writing of the results.

# Results

One hundred and fifty nine patients were enrolled in the initial 3–6 months study (Deep Brain Stimulation for Parkinson's

Disease Study Group, 2001). Of these patients, 105 were implanted in the 8 centres participating in the present study (Fig. 1). For reasons indicated in Fig. 1, 23 and furthermore, another 13 patients dropped out or were excluded from the analysis at 1 and 3 years, respectively. Three patients died because of cancer, one died after myocardial infarction and the reason for the death of one patient could not be clarified by the centre of reference. In the STN-treated group, two patients were unilaterally implanted only, and five patients required explantation of one electrode or the battery owing to local infection. Eight other patients were not available for follow-up assessment owing to refusal to continue in the protocol ($n$ = 6), psychiatric complications ($n$ = 1) and dementia ($n$ = 1). In the GPi group, eight patients remained effectively controlled with unilateral stimulation, two required electrode explantation owing to local infection and in two other patients whose response was suboptimal the stimulators were replaced in the STN in hope of obtaining better results. Three patients were not available for follow-up assessment owing to dementia ($n$ = 1), disease of spouse ($n$ = 1) and refusal ($n$ = 1).

Of the 69 bilaterally implanted patients available for assessment at 3–4 years post-operatively, 49 patients were implanted in the STN and 20 patients in the GPi. The parameters of stimulation used at 3–4 years were unchanged with respect to the ones set up in the early phases (3 months post-operatively) (Table 2) except for a 14% increment in the amplitude of stimulation for the STN-treated group ($P < 0.0001$). The majority of electrodes were programmed in monopolar for both STN (80%) and GPi (70%).

## Bilateral STN stimulation

Stimulation induced a significant improvement of 50% ($P$ = 0.00001) in the 'off' medication UPDRS-III score (Fig. 2; Table 3) with respect to baseline. The cardinal motor

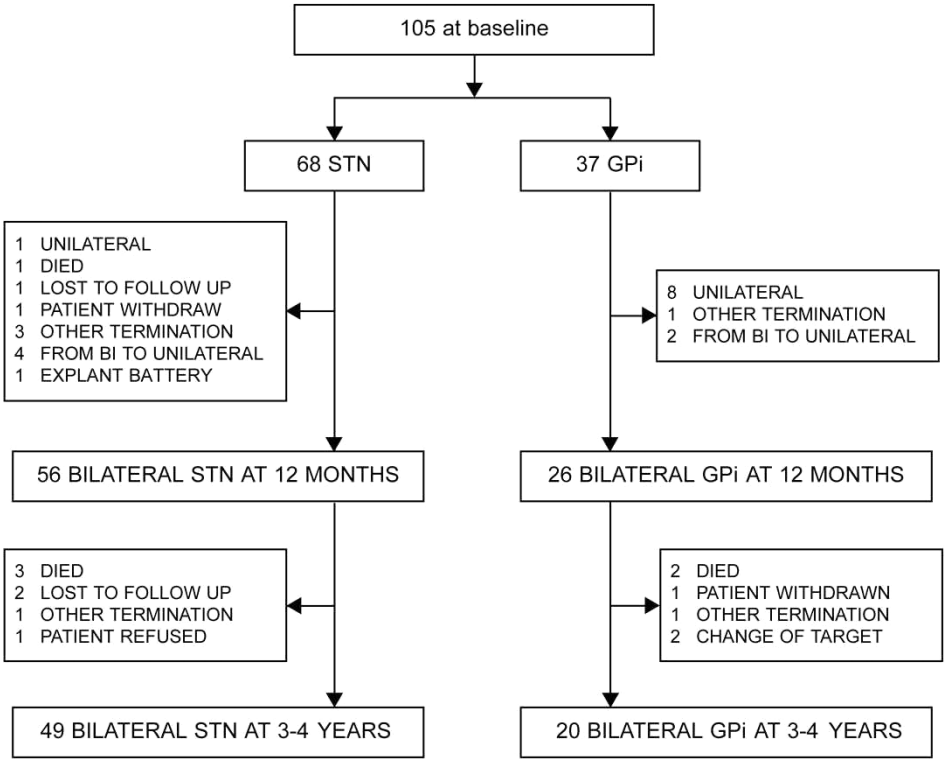


**Fig. 1** Trial profile. Patients were not randomly allocated to either STN or GPi stimulation but in accordance with best clinical judgement.

**Table 2** Parameters of stimulation at 3 months and 3–4 years follow-up

| | STN | | | GPi | | |
|---|---|---|---|---|---|---|
| | Amplitude (V) | Rate (Hz) | Pulse width (μs) | Amplitude (V) | Rate (Hz) | Pulse width (μs) |
| 3 months | 2.7 ± 0.6 (1.1–4.1) | 148 ± 22 (108–185) | 76 ± 34 (60–225) | 3.1 ± 0.8 (2.4–6.0) | 169 ± 22 (130–185) | 105 ± 44 (60–210) |
| 3–4 years | 3.1 ± 0.5* (2.2–4.0) | 151 ± 23 (90–185) | 72 ± 20 (60–150) | 3.2 ± 0.4 (2.3–3.8) | 163 ± 25 (110–185) | 115 ± 54 (60–240) |

Data presented as mean ± SD (range). *$P$ = 0.00002; 3–4 years versus 3 months.

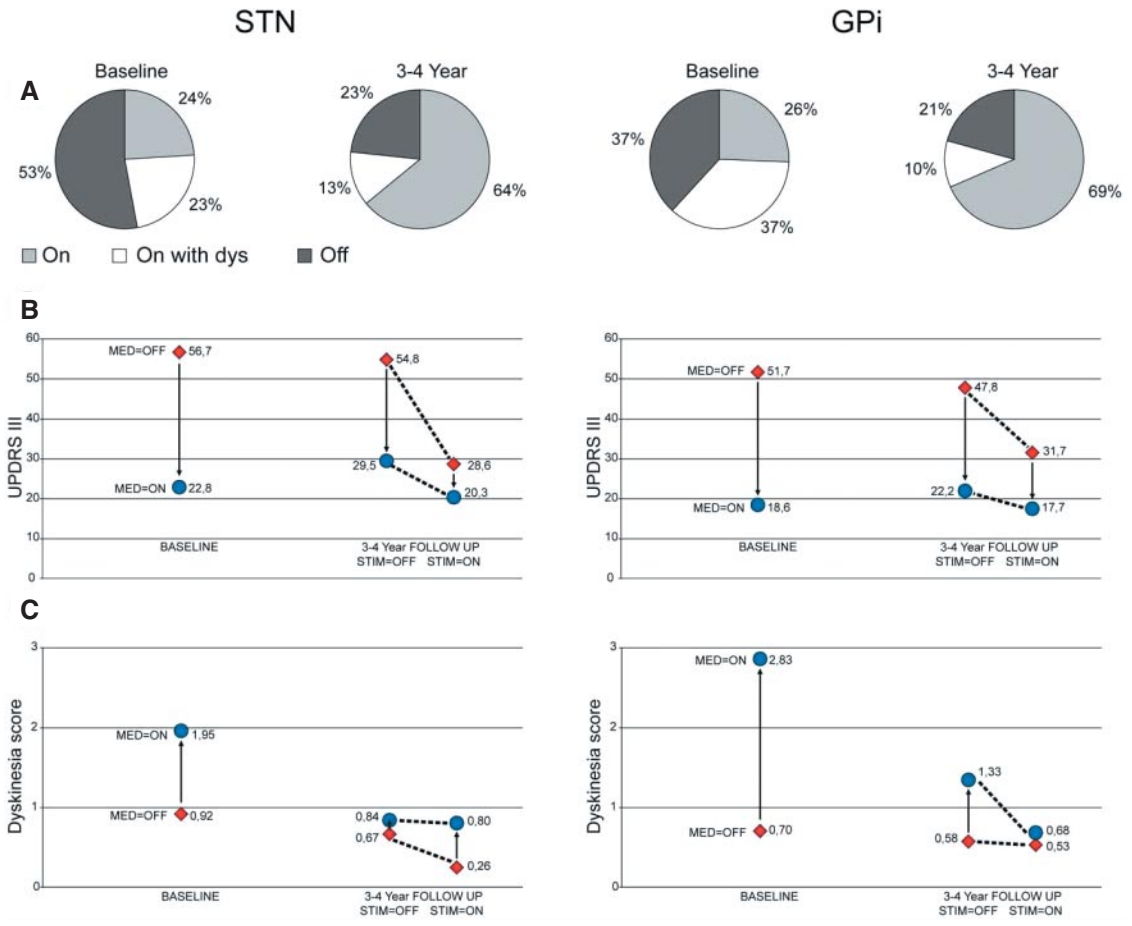


**Fig. 2** (**A**) The mean percentage of time during waking hours with bad mobility ('off'), good mobility accompanied by dyskinesias ('on' with dyskinesia) and good mobility without dyskinesias ('on') at baseline and after 3–4 years post-operatively in patients treated with stimulation of either STN ($n$ = 49) or GPi ($n$ = 20). (**B**) The UPDRS-III (motor) in the 'off' (red) and 'on' (blue) medication states preoperatively and with and without the effect of stimulation post-operatively. (**C**) The dyskinesia score shows the variation in 'off' period dystonia (red) and 'on' choreic dyskinesias (blue) preoperatively and with and without the effect of stimulation post-operatively.

**Table 3** Effect of subthalamic and pallidal stimulation on the UPDRS-III (motor) in the 'off' and 'on' medication states

| Site and conditions | Baseline | 1 year ($n$ = 47) | 3–4 years | $P$-value | |
|---|---|---|---|---|---|
| | | | | 3 years versus baseline | 3–4 years versus 1 year after surgery |
| STN ($n$ = 49) | | | | | |
| Off medication | | | | | |
| Without stimulation | 56.7 ± 15.7 | 53.7 ± 16.4 | 54.8 ± 16.5 | n.s. | n.s. |
| With stimulation | | 24.6 ± 14.9 | 28.6 ± 15.7 | <0.0001 | <0.02 |
| On medication | | | | | |
| Without stimulation | 22.8 ± 10.4 | 27.9 ± 17.2 | 29.5 ± 20.6 | $P$ < 0.02 | n.s. |
| With stimulation | | 15.9 ± 12.2 | 20.3 ± 14.7 | n.s. | <0.01 |
| GPi ($n$ = 20) | | | | | |
| Off medication | | | | | |
| Without stimulation | 51.7 ± 13.6 | 49.6 ± 17.7 | 47.8 ± 12.9 | n.s. | n.s. |
| With stimulation | | 29.2 ± 14.9 | 31.7 ± 12.8 | <0.0001 | n.s. |
| On medication | | | | | |
| Without stimulation | 18.6 ± 10.3 | 17.7 ± 14.0 | 22.2 ± 15.4 | n.s. | n.s. |
| With stimulation | | 13.5 ± 10.2 | 17.7 ± 13.0 | n.s. | <0.05 |

n.s. = not significant.

**Table 4** Effect of subthalamic stimulation on UPDRS-III total and subscores, levodopa-induced dyskinesias, and ADL off and on levodopa

| | Baseline | 1 year | 3–4 years | *P*-value | |
|---|---|---|---|---|---|
| | | | | 3–4 years versus baseline* | 3–4 years versus 1 year† |
| Off medication | | | | | |
| Total motor score (range 0–108) | 56.7 ± 15.7 | 24.6 ± 14.9 | 28.6 ± 15.7 | <0.0001 | <0.02 |
| Tremor (range 0–28) | 13.1 ± 4.3 | 2.3 ± 2.3 | 1.7 ± 3.0 | <0.0001 | n.s. |
| Rigidity (range 0–20) | 10.8 ± 3.9 | 3.8 ± 3.4 | 4.4 ± 3.5 | <0.0001 | n.s. |
| Gait (range 0–4) | 2.9 ± 1.0 | 1.4 ± 1.1 | 1.7 ± 1.2 | <0.0001 | <0.02 |
| Bradykinesia (range 0–32) | 19.9 ± 6.7 | 10.7 ± 7.2 | 11.3 ± 7.6 | <0.0001 | n.s. |
| Postural stability (range 0–4) | 2.6 ± 1.0 | 1.2 ± 1.0 | 1.8 ± 1.2 | <0.0001 | <0.001 |
| Speech (range 0–4) | 1.9 ± 1.0 | 1.4 ± 0.9 | 1.8 ± 1.0 | n.s. | <0.01 |
| Dyskinesias (range 0–4) | 0.92 ± 1.10 | 0.40 ± 0.80 | 0.26 ± 0.66 | <0.02 | n.s. |
| ADL (range 0–52) | 29.7 ± 8.0 | 14.8 ± 7.3 | 16.9 ± 8.7 | <0.0001 | <0.001 |
| On medication | | | | | |
| Total motor score (range 0–108) | 22.8 ± 10.4 | 15.9 ± 12.2 | 20.3 ± 14.7 | n.s. | <0.01 |
| Tremor (range 0–28) | 2.5 ± 3.4 | 0.8 ± 1.3 | 0.5 ± 1.2 | <0.001 | n.s. |
| Rigidity (range 0–20) | 4.5 ± 2.8 | 2.4 ± 2.7 | 2.9 ± 3.1 | <0.001 | n.s. |
| Gait (range 0–4) | 0.9 ± 0.8 | 0.9 ± 1.0 | 1.2 ± 1.1 | n.s. | <0.05 |
| Bradykinesia (range 0–32) | 8.9 ± 4.8 | 6.7 ± 5.7 | 8.1 ± 6.9 | n.s. | n.s. |
| Postural stability (range 0–4) | 1.3 ± 0.8 | 0.9 ± 10 | 1.4 ± 1.2 | <0.0001† | <0.0001 |
| Speech (range 0–4) | 1.1 ± 0.9 | 1.2 ± 0.9 | 1.6 ± 0.9 | <0.001† | <0.001 |
| Dyskinesias (range 0–4) | 1.95 ± 1.07 | 0.96 ± 0.79 | 0.80 ± 0.78 | <0.0001 | n.s. |
| ADL (range 0–52) | 10.6 ± 6.7 | 10.6 ± 6.1 | 12.4 ± 8.1 | n.s. | <0.01 |

*Improvement. †Worsening. n.s. = not significant.

subscores of UPDRS-III and the UPDRS-part II scale were improved in the 'off' medication state ($P < 0.0001$), excepting speech (Table 4). Tremor was improved by 87%, rigidity by 59%, bradykinesia by 42%, gait by 41%, postural stability by 31% and UPDRS-II (ADL) by 43%, respectively (Table 4). The 'on' medication UPDRS motor score (off stimulation) at the 3–4 years evaluation was significantly higher (i.e. worse) than at baseline (23% increment, $P < 0.02$; Table 3). Stimulation in the 'on' medication state improved the UPDRS motor score from 29.5 to 20.3 (31% $P < 0.001$). The 'on' medication–on stimulation state at 3–4 years (mean UPDRS-III score 20.3 points) was not significantly different (Table 3) from the 'on' medication score at baseline (UPDRS-III, 22.8). Specific signs that changed significantly in the 'on' medication–on stimulation state were rigidity and tremor that improved by 36 and 80% ($P < 0.001$) and speech and postural stability that worsened ($P < 0.001$) (Table 4).

The times spent in 'off' and in 'on' with dyskinesias were significantly reduced by 56 and 45% ($P < 0.00001$ and $P < 0.02$ respectively). This was associated with an increment of 271% in the time 'on' without dyskinesias ($P < 0.00001$) (Fig. 2) with respect to baseline. The severity of 'on' medication dyskinesias ($P < 0.0001$) and 'off' period dystonia ($P < 0.001$) were also significantly reduced by 59% (from 1.95 to 0.8) and 72% (from 0.92 to 0.26) (Fig. 2). Global assessment by the investigators and patients classified 42 (86%) and 40 (82%) patients as markedly and severely disabled preoperatively; at the last assessment both investigators and patients scored only 17 patients (35%) as markedly or severely disabled. Levodopa equivalents intake was reduced from a mean of 1309 ± 649 to 859 ± 659 mg/day ($P < 0.001$). Six patients had stopped taking levodopa; three of these received a dopamine agonist [two were on pergolide (1 mg daily) and one on bromocriptine, 30 mg daily].

Comparison of the improvement induced by STN stimulation at 1 year against 3–4 years evaluation (Tables 3 and 4) showed a significant worsening in the 'off' and 'on' medication motor states of the UPDRS-III, ADL, speech, postural stability and gait (Table 4). There was no significant change in levodopa daily dose (769 ± 429 and 859 ± 659 mg/day at 1 and 3 years, respectively).

## Bilateral GPi stimulation

Stimulation induced a significant improvement of 39% ($P < 0.0001$) in the 'off' medication UPDRS-III score with respect to baseline assessment (Fig. 2; Table 3). The cardinal motor subscores of UPDRS-III and the UPDRS-II (Table 5) were all improved in the 'off' medication state ($P < 0.02$) except for postural stability and speech. Tremor was improved by 85%, rigidity by 38%, bradykinesia by 30%, gait by 28% and UPDRS-II (ADL) by 28%. The 'on' medication (off stimulation) UPDRS-III at 3–4 years showed a modest (22.2 versus 18.6, $P > 0.05$) worsening with respect to baseline. At 3–4 years, stimulation in the 'on' medication state improved the motor UPDRS score from 22.2 (off stimulation) to 17.7 (on stimulation) (20% $P < 0.01$). The 'on' medication–on stimulation state UPDRS-III at 3–4 years

**Table 5** Effect of pallidal stimulation on UPDRS-III total and subscores, levodopa-induced dyskinesias, and ADL off and on levodopa

| | Baseline | 1 year | 3–4 years | *P*-value | |
|---|---|---|---|---|---|
| | | | | 3–4 years versus baseline* | 3–4 years versus 1 year† |
| Off medication | | | | | |
| Total motor score (range 0–108) | 51.7 ± 13.6 | 29.2 ± 14.9 | 31.7 ± 12.8 | <0.0001 | n.s |
| Tremor (range 0–28) | 11.3 ± 3.0 | 2.7 ± 2.1 | 1.7 ± 1.3 | <0.02 | n.s |
| Rigidity (range 0–20) | 10.9 ± 3.8 | 6.5 ± 3.8 | 6.8 ± 3.3 | <0.001 | n.s |
| Gait (range 0–4) | 2.5 ± 1.0 | 1.5 ± 1.2 | 1.8 ± 1.3 | <0.02 | n.s |
| Bradykinesia (range 0–32) | 18.3 ± 4.6 | 10.9 ± 6.1 | 12.9 ± 6.0 | <0.02 | n.s. |
| Postural stability (range 0–4) | 2.3 ± 1.1 | 1.4 ± 1.1 | 1.7 ± 1.1 | n.s. | n.s. |
| Speech (range 0–4) | 1.5 ± .08 | 1.3 ± 0.9 | 1.5 ± 0.7 | n.s. | n.s |
| Dyskinesias (range 0 –4) | 0.70 ± 1.15 | 0.33 ± 0.84 | 0.53 ± 0.77 | n.s | n.s |
| ADL (range 0–52) | 26.8 ± 8.9 | 18.1 ± 9.2 | 19.2 ± 10.0 | <0.02 | n.s |
| On medication | | | | | |
| Total motor score (range 0–108) | 18.6 ± 10.3 | 13.5 ± 10.2 | 17.7 ± 13.0 | n.s. | <0.05 |
| Tremor (range 0–28) | 1.9 ± 2.5 | 0.4 ± 0.9 | 0.4 ± 1.0 | n.s. | n.s. |
| Rigidity (range 0–20) | 2.8 ± 4.0 | 2.4 ± 3.4 | 2.7 ± 3.2 | n.s. | n.s. |
| Gait (range 0–4) | 1.2 ± 1.0 | 0.7 ± 0.9 | 1.1 ± 1.2 | n.s. | <0.05 |
| Bradykinesia (range 0–32) | 7.2 ± 4.3 | 5.4 ± 4.3 | 7.8 ± 6.3 | n.s. | n.s. |
| Postural stability (range 0–4) | 1.3 ± 0.9 | 0.9 ± 0.9 | 1.2 ± 1.3 | n.s. | n.s. |
| Speech (range 0–4) | 0.9 ± 0.8 | 0.8 ± 0.9 | 1.1 ± 1.0 | n.s. | n.s. |
| Dyskinesias (range 0–4) | 2.83 ± 1.18 | 0.80 ± 0.62 | 0.68 ± 0.75 | <0.0001 | n.s. |
| ADL (range 0–52) | 12.0 ± 7.2 | 8.8 ± 7.6 | 12.2 ± 10.0 | n.s. | <0.02 |

*Improvement. †Worsening. n.s. = not significant.

was 17.7 compared with an 18.6 'on' score before stimulator implantation (Table 3). There was no stimulation-induced improvement in the cardinal features in the 'on' medication condition (Table 5).

The times spent in 'off' and 'on' with dyskinesias were significantly reduced by 45% ($P < 0.002$) and 72% ($P < 0.0001$) and the time spent in 'on' without dyskinesias was increased by 169% ($P < 0.00001$) (Fig. 2). Dyskinesia severity was significantly reduced by 76% (from 2.83 to 0.68) ($P = 0.0001$) and there was no change in 'off' period dystonia (Fig. 2; Table 5). Preoperatively, global assessment by the investigators and patients scored 14 (70%) and 15 patients (75%), respectively as markedly and severely disabled compared with 6 (30%) and 7 patients (35%) post-operatively. Daily levodopa equivalents were not significantly modified (1074 ± 462 mg preoperatively and 1418 ± 1254 mg post-operatively, $P = 0.22$). One patient had stopped taking levodopa and continued treatment with bromocriptine (22.5 mg/daily).

Comparison between the improvement induced by GPi stimulation at 1 and 3–4 years is summarized in Tables 3 and 5. There was a significant worsening in the 'on' medication–on stimulation state in the UPDRS-III ($P < 0.05$), gait ($P < 0.05$) and ADL ($P < 0.02$). There was no significant change in levodopa daily dose (1242 ± 528 and 1418 ± 1252; $P = 0.62$) between the 1 and 3 years assessments.

## Adverse events

A total of 58 persistent AEs were reported in 26 (53%) of the 49 patients in the STN-treated group and 8 AEs were encountered in 7 (35%) of the 20 patients in the GPi-treated group. Seven patients (six from the STN group and one from the GPi group) required another surgery to treat device-related complications, such as lead fracture or infection of the connection and cable, skin erosion or infection at the site of the battery, and 11 patients had 17 batteries changed during this period. In 2 patients infections of the device led to discontinuation of treatment with DBS. The most frequent and clinically relevant AEs (classified in five categories) at the time of the 3–4 year evaluation are listed in Table 6. All but two of these AEs occurred in patients treated with STN stimulation. The remaining five patients in the GPi group experienced AEs, such as sleep difficulty, hypersexuality, dyskinesias and increased parkinsonism that were reported as severe or clinically relevant in 4 cases. The majority of such AEs were reported as unrelated to stimulation. Severe psychiatric disturbances was reported in one patient from the STN group. Speech disturbances (scored in UPDRS-III) were relatively frequent, being judged as severe in five patients (4 STN and 1 GPi). The severity of AEs did not warrant suspension of DBS in any case.

## Discussion

We report a 3–4 year follow-up evaluation of the effect of DBS of STN or GPi in patients with advanced Parkinson's disease inadequately controlled with available pharmacological treatments. The main findings are that the beneficial anti-parkinsonian effects of DBS in both these sites persisted

**Table 6** Number of major AEs present 3–4 years after surgery

| | STN* | | | | GPi† | | | |
|---|---|---|---|---|---|---|---|---|
| | AE *N* | Mild *n* of AE | Moderate *n* of AE | Severe *n* of AE | AE *N* | Mild *n* of AE | Moderate *n* of AE | Severe *n* of AE |
| Cognition | 12 | 4 | 7 | 1 | 1 | 1 | 0 | 0 |
| Memory decline | | | | | | | | |
| Psychiatric disturbances | | | | | | | | |
| Depression | 3 | 0 | 3 | 0 | – | – | – | – |
| Apathy | | | | | | | | |
| Anxiety | | | | | | | | |
| Mood disturbances | | | | | | | | |
| Speech difficulties | 9 | 2 | 3 | 4 | 1 | 0 | 0 | 1 |
| Dysphonia | | | | | | | | |
| Dysarthria | | | | | | | | |
| Dysequilibrium | 8 | 2 | 5 | 1 | – | – | – | – |
| Falls | | | | | | | | |
| Balance disturbances | | | | | | | | |
| Gait disorders | 9 | 2 | 3 | 4 | – | – | – | – |
| Total | 41 | 10 | 21 | 10 | 2 | 1 | 0 | 1 |
| Severity (% of total AE) | 100 | 24.4 | 51.2 | 24.4 | 100 | 50 | | 50 |

*$N$ patients = 49/$N$ patients with AE = 26. †$N$ patients = 20/$N$ patients with AE = 7.

after a relatively prolonged follow-up period of 3–4 years. DBS particularly improved the 'off' drug parkinsonian state (Fig. 2). The motor scores in the 'off' state were significantly reduced by stimulation, leading to a dramatic amelioration of the frequency and severity of 'off' periods, and dyskinesias were also significantly improved. In practice, the addition of stimulation to medication, which was significantly reduced only in the STN group, resulted in patients experiencing adequate mobility for a much larger proportion of the day along with a significant improvement in the ability to perform daily living activities. The cardinal motor features of Parkinson's disease (tremor, rigidity, bradykinesia and gait) remained significantly improved in both groups at 3–4 years except for postural stability in the GPi group and speech in both groups. This benefit is all the more remarkable considering that patients included in this study had already developed severe motor complications as typically seen in relatively advanced Parkinson's disease. Thus, DBS of STN or GPi showed a marked capacity to improve motor features in Parkinson's disease further supporting the paramount importance of the STN–GPi projection in the pathophysiology of Parkinson's disease. Such effects probably require an adequate selection of the surgical candidates, appropriate recognition of the target and placement of the electrodes in the intended positions and expertise in the adjustment of stimulation and medication post-operatively. Failure to fulfil any of these crucial aspects will probably explain relatively poor results (Ford *et al.*, 2004).

Comparison of the UPDRS-III scores in the 'off' medication state obtained at baseline with the one at 3–4 years in the 'off' medication and off stimulation condition revealed no significant difference in either the STN or GPi treated groups. This result could be taken at first to suggest a potential effect of DBS on disease progression. However, we do not believe the design of this study allows posing such proposal. There are several uncontrolled factors, such as the long-lasting effect of medication, which are now recognized to last longer than 12–24 h and that examinations took place after turning off DBS for 1–2 h which is known to be insufficient to clear completely the effect of stimulation (Temperli *et al.*, 2003). Moreover, a significant deterioration in the effect of stimulation in the 'off' drug state for the STN group was observed between the first year and last evaluations (Table 3). This was mainly owing to deterioration of gait, postural stability and speech (Table 4). More importantly perhaps, in both groups we observed worsening of the UPDRS-III, gait and ADL in the 'on' medication state (Tables 4 and 5) despite a modest (non-significant) increment in the mean daily levodopa dose. This decline between the first year and the longer-term follow-up is similar to the experience reported by the Grenoble group who reported a decline in the response to both stimulation and levodopa of akinesia, speech, postural stability and gait in 42 patients treated with STN stimulation for 5 years (Krack *et al.*, 2003). In our STN-treated group, there was also a predominant deterioration of axial features in the 'off' medication–on stimulation state as well as in the 'on' medication–on stimulation state. Admittedly, this effect was less striking for patients in the GPi group, who did not exhibit any significant deterioration in the 'off' medication state throughout the follow-up period. This may, in part, be related to the fact that GPi patients were receiving a larger (+39%) daily levodopa dose at the last evaluation than the STN-treated group. It is well known that motor scores obtained after only 12 h of drug abstinence are influenced by the 'long duration response' to levodopa and this is a dose-dependent effect (Fahn *et al.*, 2004). There may be other

factors, such as predominant clinical features (e.g. the GPi group exhibited greater dyskinesias score than the STN group) and size of the groups, that may account for the observed difference and were not controlled in this study.

The accumulated experience indicates that both levodopa and DBS are capable of improving and controlling to a large extent akinesia, rigidity and tremor which are recognized as the genuine expression of cell loss in the substantia nigra compacta leading to dopamine deficiency in the posterior putamen (Kisch *et al.*, 1988). However, reduced responsiveness to levodopa of axial motor signs is a well-recognized feature of advanced Parkinson's disease (Muller *et al.*, 2000). It is, thus, most likely that the observed reduction in the beneficial effect of DBS reflects disease progression and extension of the pathological process beyond the nigro-striatal dopaminergic system (Lang and Obeso 2004). These findings should be taken in consideration when planning future studies regarding the optimal period in Parkinson's disease evolution for surgical treatment with DBS.

The patients reported here are the 'survivors' of the initial cohort of the multicentre study. Accordingly, the real therapeutic value of DBS in advanced Parkinson's disease needs to take into account the risk of intracranial haemorrhage associated with surgery (~2%) (Umemura *et al.*, 2003) and the risk of permanent neurological deficit (2.8%) in this series (Deep Brain Stimulation for Parkinson's Disease Study Group, 2001). Also noteworthy in this regard are complications related to the implant, such as infections, skin erosions and lead breakage (Oh *et al.*, 2002; Lyons *et al.*, 2004), which led to discontinuation of treatment in seven patients (6.1%). The rate of AEs recorded at 3–4 years was high, particularly for patients implanted in the STN. These complications consisted mainly of cognitive impairment and psychiatric manifestations (hallucinations, delirium, etc.), mood disturbances and speech, gait and equilibrium problems (Table 6). Such AEs are frequently encountered in advanced Parkinson's disease patients treated with drugs alone (Muller *et al.*, 2000; Lang and Obeso, 2004), and it is therefore difficult to judge to what extent chronic DBS contributed to their origin. However, AEs were more frequent in the STN-treated group compared with the GPi group, which implies some specificity to the findings. Whether or not this is directly related to a differential effect of surgery on the STN and GPi, or to other factors, cannot be resolved at this time, since the study was not a randomized controlled trial comparing the two targets. Importantly, AEs were not considered severe enough, in the face of clinically valuable benefit, to withdraw DBS in any patient.

It would be desirable to recognize conclusively the advantages and disadvantages of DBS of STN or GPi. Overall, the therapeutic benefit was similar for the two surgical targets. DBS of the STN conveys a significant reduction in levodopa daily dose that was not observed in patients in the GPi group. However, side-effects were less frequently encountered in patients treated with pallidal stimulation. Further studies will be needed to allow appropriate judgement of which target is more adequate or which clinical presentations may be better controlled with either target. In conclusion, DBS of STN or GPi is capable of improving patients with advanced Parkinson's disease for a period of at least 3–4 years. The long-term AEs associated with this technique are considered acceptable for a population with such advanced disability. This study represents the first worldwide multicentre trial conducted with DBS of STN or GPi. Several of the participating teams had no prior experience with the procedure when they began enrolling patients, so conceivably better clinical results, and a more optimal therapeutic profile, might be achieved nowadays owing to better selection of patients, more adequate training of the personnel involved in the surgical and post-operative procedures, and advances in stereotactic techniques (Welter *et al.*, 2002).

*Conflict of interest statement*: All authors have occasionally received honoraria from Medtronic for lecturing at meetings. The three members of the *ad hoc* AE Committee were reimbursed by Medtronic for their time spent collating the AE data but not for their activity in preparing this paper.

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## Appendix 1

The following investigators participated in the study: Paris: Y.A., A. M. Bonnet, P. Cornu, D. Dormont, J.-L.H., V. Mesnage, B.P., M. L. Welter; Lund: R. Ekber, G. Kullberg, S. Rehncrona, L Törnqvist; Pamplona: A. Aristu, J.G., J. Irigoyen, J.A.O., M.C.R.-O., I.Z; Grenoble: A.-L.B., V.F., P.P., N.V.B., J.X; Toronto: R. Kumar, A. E. Lang, A.M.L., E. Sime, J.S.-C, F. Khan, G. Kleiner-Fisman, L. Del Rizzo; Düsseldorf: V. Sturm, J.V; Barcelona: A.G., J. Kulisevski; J. Mulet, B.P.-S; Rome: A.A., M. F. Contarino, E. Moro, L.R. and M.S.

## Appendix 2

Members of the *ad hoc* Adverse Events Committee: M. Hariz (London), N.P. Quinn (London), J. Speelman (Amsterdam).