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# Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants

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**Deep brain stimulation of the subthalamic nucleus represents the most important innovation for treatment of advanced Parkinson's disease. Prospective studies have shown that although the beneficial effects of this procedure are maintained at 5 years, axial motor features and cognitive decline may occur in the long term after the implants. In order to address some unsolved questions raised by previous studies, we evaluated a series of 20 consecutive patients who received continuous stimulation for 8 years. The overall motor improvement reported at 5 years (55.5% at Unified Parkinson's Disease Rating Scale—motor part, $P<0.001$ compared with baseline) was only partly retained 3 years later (39%, $P<0.001$, compared with baseline; −16.5%, $P<0.01$, compared with 5 years), with differential effects on motor features: speech did not improve and postural stability worsened ($P<0.05$). The preoperative levodopa equivalent daily dose was reduced by 58.2% at 5 years and by 60.3% at 8 years. In spite of subtle worsening of motor features, a dramatic impairment in functional state (−56.6% at Unified Parkinson's Disease Rating Scale—Activities of Daily Living, $P<0.01$) emerged after the fifth year of stimulation. The present study did not reveal a predictive value of preoperative levodopa response, whereas few single features at baseline (such as gait and postural stability motor scores and the preoperative levodopa equivalent daily dose) could predict long-term motor outcome. A decline in verbal fluency (slightly more pronounced than after 5 years) was detected after 8 years. A significant but slight decline in tasks of abstract reasoning, episodic memory and executive function was also found. One patient had developed dementia at 5 years with further progression at 8 years. Executive dysfunction correlated significantly with postural stability, suggesting interplay between axial motor deterioration and cognition. Eight years after surgery, no significant change was observed on scales assessing depression or anxiety when compared with baseline. At 8 years, there was no significant increase of side-effects when compared with 5-year follow-up. In conclusion, deep brain stimulation of the subthalamic nucleus is a safe procedure with regard to cognitive and behavioural morbidity over long-term follow-up. However, the global benefit partly decreases later in the course of the disease, due to progression of Parkinson's disease and the appearance of medication- and stimulation-resistant symptoms.**

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**Keywords:** Parkinson's disease; DBS; cognition; motor; postural control

**Abbreviations:** DBS = deep brain stimulation; LEDD = levodopa-equivalent daily dose; MWCST = Modified Wisconsin Card Sorting Test; RAVLT = Rey's Auditory Verbal Learning Test; RPM '47 = Raven's Progressive Matrices; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale

# Introduction

The treatment of advanced stages of Parkinson's disease is a major challenge for modern medicine. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) represents the most important innovation for treatment of advanced Parkinson's disease since the discovery of levodopa (Limousin *et al.*, 1995). Numerous studies, including randomized controlled trials, have demonstrated that this procedure can dramatically improve the motor condition of patients with motor fluctuations and dyskinesias (Deuschl *et al.*, 2006; Weaver *et al.*, 2009). There is abundant information on the short-term outcome (6–12 months postoperatively) of implanted patients (Limousin and Martinez-Torres, 2008), and sufficient information on medium-term results (up to 5 years postoperatively), either for motor (Krack *et al.*, 2003; Schupbach *et al.*, 2005; Piboolnurak *et al.*, 2007; Wider *et al.*, 2007; Gervais-Bernard *et al.*, 2009; Romito *et al.*, 2009; Simonin *et al.*, 2009) or cognitive outcome (Contarino *et al.*, 2007). The medium-term effect of STN stimulation provides sustained and marked improvement of the dopaminergic-responsive motor symptoms with reduction of severity and duration of dyskinesias and OFF-periods compared with the pre-implant state. Dopaminergic medication is markedly reduced after implant (Romito *et al.*, 2009), contributing to dyskinesia reduction (Bejjani *et al.*, 2000*a*; Oueslati *et al.*, 2007).

Disease progression in Parkinson's disease causes a gradual involvement of non-dopaminergic motor circuits, with the appearance of axial motor features and of non-motor symptoms that do not respond to standard antiparkinsonian medication (Braak and Del Tredici, 2008; Devos *et al.*, 2010). There is also preliminary evidence that axial motor features (mainly deterioration of speech, postural impairment and freezing) and cognitive decline may occur in the long term after STN implants (Krack *et al.*, 2003; Funkiewiez *et al.*, 2004; Schupbach *et al.*, 2005; Contarino *et al.*, 2007; Wider *et al.*, 2007). Medium-term studies have shown that although the beneficial effect of STN-DBS is maintained at 5 years, patients still experience worsening of symptoms due to disease progression; therefore, autonomy in daily living activities is maintained but not improved (Romito *et al.*, 2009). The questions raised by mid-term follow-up studies concern three aspects: (i) the long-term motor outcome of symptoms that improve in the short- and medium term with STN-DBS; (ii) the identification of predictors of long-term motor outcome; and (iii) the long-term behavioural and cognitive outcome. These issues are addressed by the present study, which provides long-term assessment of patients who underwent STN-DBS 8 years previously.

# Material and methods

We studied a series of consecutive patients who underwent STN implants at the Policlinico Gemelli hospital in Rome between 1996 and 2001 and received continuous stimulation for 8 consecutive years. A total of 32 patients with Parkinson's disease received STN-DBS implants (Table 1); 20 of them completed the 8-year observation period and were included in the study. They consisted of eight females; ages at implant and disease duration were 56.9 ± 7.2 and 13.7 ± 4.8 years, respectively; the mean follow-up was 96 ± 3.1 months. All patients had a diagnosis of Parkinson's disease according to the United Kingdom Parkinson's Disease Brain Bank criteria (Hughes *et al.*, 1992). At inclusion, all patients were in Hoehn-Yahr stage ≥III in the practically defined OFF condition, had sustained response to levodopa with motor complications, such as disabling motor fluctuations with prolonged and at least occasionally unpredictable OFF periods (patients spent ≥25% of the waking day in the OFF state) and ON-state dyskinesias, and fulfilled the inclusion and exclusion criteria proposed by the core assessment programme for surgical interventional therapies in Parkinson's disease panel (Defer *et al.*, 1999). Exclusion criteria were as follows: (i) heart pacemaker bearer; (ii) unstable drug regimen; (iii) moderate to severe cognitive impairment according to cognitive evaluations (score <20 on the Mini Mental State Examination); (iv) dementia, as defined by Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000); (v) ongoing severe psychiatric symptoms (e.g. persistent hallucinations, psychosis and sustained depression); (vi) prior brain surgery; (vii) an unsatisfactory general condition; or (viii) an inability to comply with the study protocol.

**Table 1 Patients' characteristics at baseline (± SD)**

| | Completed the 8-year stimulation period | Did not complete the period | Total |
|---|---|---|---|
| Number | 20 | 12 | 32 |
| Gender (male/female) | 12/8 | 6/6 | 18/14 |
| Age at implant (years) | 56.9 ± 7.2 | 57.0 ± 7.6 | 56.9 ± 7.3 |
| Disease duration at implant (years) | 13.7 ± 4.8 | 14.5 ± 7.0 | 14.0 ± 5.5 |
| Follow-up (months) | 96 ± 3.1* | 27.4 ± 19.0* | 70.3 ± 35.6 |

*$P < 0.01$.

The study protocol was approved by the local ethical committee. The eligible patients signed an informed consent before entering the study.

## Surgical and perioperative procedures

Bilateral simultaneous STN implants were performed in all patients using a standard stereotactic technique (Moro *et al.*, 1999). Intraoperative test stimulation (pulses of 60 μs at a frequency of 130 Hz) was performed by a neurologist while the patient was awake before implanting the permanent stimulating electrode. Approximately 1 week later, two single-channel (Itrel II or Soletra, Medtronic, Minneapolis, MN, USA) or one double-channel (Kinetra, Medtronic, Minneapolis, MN, USA) implantable pulse generators were placed in the subclavear region. Stimulation parameters were then checked without medication, in order to achieve optimal control of motor symptoms and to identify the threshold for side-effects. Dopaminergic medication was reintroduced, if required, and was maintained to the minimum level sufficient to achieve optimal motor control.

## Motor assessment

Patients were evaluated preoperatively (at baseline) and then re-evaluated at 6 months, and 1, 3, 5, 6 and 8 years post-implant. Preoperative evaluations were performed in the morning, in the practically defined OFF condition (Defer *et al.*, 1999) and in the best ON condition following the administration of a dose of standard liquid levodopa that was 50% higher than the usual morning dose of dopaminergic treatment. For postoperative assessment, the following conditions were considered: (i) 'Condition A': without antiparkinsonian medication and with stimulation; and (ii) 'Condition B': with both medication and stimulation. This latter condition was performed by administering an acute challenge of liquid levodopa that was 50% higher than the usual morning dose of dopaminergic treatment; for patients not taking any dopaminergic therapy, the administered levodopa dose was 250 mg. At each postoperative visit the stimulation settings were reviewed and changed, if necessary, according to a standard protocol (Krack *et al.*, 2002; Volkmann *et al.*, 2002). The number and type of changes at 5-, 6- and 8-year visits were reported.

The efficacy of STN stimulation on motor symptoms was defined as the variation between the preoperative OFF medication condition and postoperative 'Condition A'; the efficacy of combined treatment on motor symptoms was defined as the variation between the Unified Parkinson's disease Rating Scale (UPDRS) motor score in the preoperative OFF medication condition and the same score under 'Condition B'; the efficacy of combined treatment on functional state was defined as the variation between the UPDRS activities of daily living score in the preoperative ON medication condition and the same score under 'Condition B'; the efficacy of medication superimposed to stimulation was defined as the variation of motor symptoms between the preoperative OFF medication condition and the difference between postoperative 'Condition B' and postoperative 'Condition A'. These variables were chosen as they altogether provide reliable information on the patients' motor state, without exposing them to the long-lasting stimulation withdrawal required to reach a baseline off stimulation condition (Temperli *et al.*, 2003).

The motor assessment was performed using the motor section of the UPDRS (Fahn *et al.*, 1987). Upper limb akinesia was defined as the sum of the following UPDRS motor items: finger and hand tapping (Items 23 and 24), and hand pronation–supination (Item 25). Lower limb akinesia was determined using the UPDRS foot tapping subscore (item 26). Bradykinesia was determined using UPDRS item 31. Gait (item 29) and postural stability (item 30) were analysed as individual outcomes, and the total axial score was composed by adding these two items to speech (item 18). The levodopa-equivalent daily dose (LEDD) was expressed in milligrams and computed according to standard conversion factors (Romito *et al.*, 2002); the total electrical energy delivered on each side by the stimulator was measured in microjoules, according to a standard formula (Koss *et al.*, 2005).

Adverse events were systematically collected from the patients and caregivers and were classified as transient, persistent (if not improved by turning off the stimulator for a short time), stimulation induced (present at optimal stimulation parameters, but improved when the stimulator was turned off or stimulation parameters were modified), device-related or unrelated to the procedure or stimulation (Romito *et al.*, 2002).

## Cognitive and behavioural assessment

Cognitive assessment was carried out by means of an extensive neuropsychological test battery described previously (Daniele *et al.*, 2003), including the Mini Mental State Examination, tasks of spatial (Corsi's block-tapping test forward and backward) and verbal (digit span forward and backward) short-term memory, episodic verbal memory [subtests of immediate and delayed recall of the Rey's Auditory Verbal Learning Test (RAVLT)], non-verbal abstract reasoning [Raven's Progressive Matrices (RPM'47)], phonological verbal fluency and a task assessing frontal cognitive functions such as cognitive flexibility [Modified Wisconsin Card Sorting Test, (MWCST)]. Tests sensitive to motor speed were not included in the neuropsychological battery to minimize the possible effects of motor performance (bradykinesia or dyskinesias) on cognitive assessment. The raw scores obtained by each patient were considered for by-group analysis; the raw scores were also adjusted for age and educational level in each patient, for further analysis.

Cognitive assessment and a clinical interview, aimed at detecting the presence of behavioural abnormalities or psychiatric disorders, were performed preoperatively (during the week preceding electrode implantation) and postoperatively 5 and 8 years after implantation. In addition, an evaluation of mood and anxiety by means of Zung's self-rating depression scale (Zung, 1965) and self-rating anxiety scale (Zung, 1971), which can quantify symptoms of depression and anxiety, was carried out preoperatively and 8 years after implantation.

All cognitive and behavioural assessments before and after surgery were performed while the patients were on antiparkinsonian medication. Postoperative cognitive and behavioural assessments were performed with stimulators turned on.

## Neuropathological evaluation

The neuropathological evaluation, in case of death of a patient during the study period, included the following procedures: immersion-fixing of the explanted brain in 10% formalin for 2 weeks, then tissue blocks sampling from different brain regions containing lead track, lead tip and area involved by stimulation. Several brain slices were obtained. Tissue samples were embedded in paraffin and sections cut and stained serially to allow the tip of the lead to be localized. Sections of cerebrum, brainstem and cerebellum were examined using routine histological stains and immunocytochemistry for glial fibrillary acidic protein, ubiquitin and synuclein to provide a histological diagnosis.

## Statistical analyses

Continuous data comparing baseline and postoperative motor scores were analysed by means of the Student's *t*-test (unpaired and paired) or the Wilcoxon signed-rank test, according to data distribution. Survival analyses were performed by means of the Kaplan–Meier product-limit method, to describe the rate of progression of axial symptoms until the patients reached a meaningful worsening of gait or postural stability. These were defined as a condition in which a patient reached scores $\geq 2$ for gait or $\geq 3$ for postural stability in the best postoperative motor condition (under both medication and stimulation).

To evaluate group outcome on all cognitive and behavioural measures, the scores obtained on each postoperative assessment were compared with preoperative scores by means of the Wilcoxon's signed-rank test. Given the explorative nature of our study, the standard non-corrected significance $\alpha$ level of $P<0.05$ was used to reduce the risk of a type II error. To assess postoperative changes among individual patients on cognitive and behavioural variables (individual outcome), each individual postoperative raw score was transformed to a standard *z*-score, using means and standard deviation values of the sample at baseline. The criterion of an increase of more than +1.0 SD was used to register individual postoperative improvements, while a decrease of >1.0 SD was used to register individual postoperative declines (Trepanier *et al*., 1998). Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) software (http://www.spss.com/spss/ release 12.0).

# Results

Of the 32 patients with Parkinson's disease, 3 patients died from causes unrelated to the DBS procedure (intestinal cancer, intraocular melanoma and pulmonary embolism); 2 patients were lost to follow-up because of difficulties in reaching our centre for scheduled evaluations; 3 patients discontinued the study after one electrode was removed (see adverse events) and re-implanted some months later. Four patients did not reach the 8-year visit and are currently being followed up. Four patients who received motor assessment were not available for cognitive testing at 8 years.

A post-mortem examination was obtained for one patient who died 1 year after implant. Neuropathology confirmed the histological diagnosis of idiopathic Parkinson's disease with severe neuronal depletion in the substantia nigra and occasional Lewy bodies identified in the remaining neurons. On the right side, the electrode reached the subthalamic nucleus with contact 0 and the tip abutted the red nucleus; on the left side, the electrode was located into the subthalamic nucleus, with the tip abutting its ventral border.

## Motor outcome

The motor efficacy of STN stimulation was 55.5% at 5 years ($P<0.001$, compared to baseline) and 39% at 8 years ($P<0.001$, compared to baseline; $P<0.01$, compared to 5 years). Most parkinsonian features improved after 8 years of stimulation when compared with the condition before implant, albeit to a variable degree: rigidity showed the most remarkable improvement (99%, $P<0.001$), followed by rest tremor (92%, $P<0.001$), postural tremor (48%, $P<0.001$), gait (41%, $P<0.01$), bradykinesia (34%, $P<0.001$), lower limb akinesia (28%, $P<0.01$) and upper limb akinesia (24%, $P<0.05$). In contrast, speech was not improved and postural stability worsened ($P<0.05$; Table 2). The comparison of outcomes at 8 versus 5 years after implant showed that resting tremor, rigidity, speech and gait did not significantly differ, while all other symptoms had worsened at 8 years.

The efficacy of combined treatment on motor symptoms was 64% after 5 years ($P<0.001$, compared with baseline) and 54.8% after 8 years ($P<0.001$). All motor items improved at 5 years with the exception of speech. At 8 years, neither speech or postural stability were improved. The comparison of outcomes at 8 versus 5 years after implant showed that postural tremor and bradykinesia had worsened, whereas all other items did not significantly differ (Table 2).

Five years after implant, 45% of patients had a clinically meaningful worsening of gait (as revealed by a score $\geq 2$ on the 'gait' item in the best postoperative motor condition, see 'Material and methods' section); 3 years later, this percentage was unchanged. In contrast, improvement of postural stability was retained at 5 years, but worsened in 35% of the patients at 8 years (as defined by a score $\geq 3$ on the 'postural stability' item). Survival analysis confirmed that gait worsening developed gradually during the course of the disease, while postural instability could be appreciated only after the 5-year assessment.

As compared with the baseline preoperative condition, the efficacy of combined treatment on functional state after 5 years was a 20.8% improvement in the UPDRS-activities of daily living score, which was not statistically significant. Eight years after surgery, the UPDRS activities of daily living score worsened by 56.6% ($P<0.01$), compared to preoperative baseline.

The efficacy of medication superimposed on stimulation at 8 years provided an average additional 34.8% improvement of the motor score ($P<0.05$). This improvement was particularly marked on rigidity (57.5%, $P<0.05$) and upper limb akinesia (32.1%, $P<0.05$), but not significant on the remaining motor features. A comparison of the efficacy of medication superimposed on stimulation between 5 and 8 years after implant did not reveal significant differences.

## Cognitive and behavioural outcome

Cognitive data were analysed for 16 patients 8 years after treatment. One additional patient had developed dementia at 5 years with further progression at 8 years. Her data were not included in this analysis. Compared to baseline, 5 years after surgery there was a significant decline in the letter verbal fluency task and in RPM '47, and a marginally significant decline in the episodic memory task (delayed recall of the RAVLT). Eight years after surgery, there was a significant decline in the letter verbal fluency task, RPM '47, the episodic memory task (immediate recall and delayed recall of the RAVLT) and in the MWCST as to the number of correct criteria. Analysis of individual data showed that in 13 out of 17 patients such cognitive decline at 8 years was mild

**Table 2 Efficacy of stimulation and progression of motor signs in all 20 patients, evaluated at different times after STN implant (± SD)**

| UPDRS motor score | Baseline | 1 year | 3 years | 5 years | 8 years |
|---|---|---|---|---|---|
| Efficacy of STN stimulation | | | | | |
| Total | 59.5 ± 9.6 | 27.6 ± 13.8* | 30.4 ± 12.0* | 26.5 ± 12.4* | 36.3 ± 11.7*,§§§ |
| Resting tremor | 7.2 ± 6.3 | 1.1 ± 2.9* | 0.9 ± 1.7* | 0.5 ± 1.2* | 0.6 ± 0.8 * |
| Postural tremor | 5.2 ± 1.8 | 1.8 ± 1.4* | 1.9 ± 1.4* | 1.7 ± 1.5* | 2.7 ± 1.7*,§§ |
| Rigidity | 10.7 ± 3.5 | 6.0 ± 3.9* | 6.8 ± 4.1* | 4.8 ± 3.9* | 5.8 ± 3.0* |
| Upper limb akinesia | 13.8 ± 4.3 | 8.6 ± 5.7* | 9.0 ± 4.8* | 7.7 ± 4.8* | 10.5 ± 3.7*,§§ |
| Lower limb akinesia | 5.3 ± 2.2 | 2.6 ± 2.5* | 2.9 ± 2.0* | 2.8 ± 2.0* | 3.8 ± 1.9*,§§ |
| Bradykinesia | 3.2 ± 0.9 | 1.3 ± 1.0* | 1.5 ± 0.8* | 1.4 ± 0.7* | 2.1 ± 0.8*,§§§ |
| Total axial | 6.0 ± 2.0 | 2.9 ± 1.3* | 3.9 ± 1.8* | 3.9 ± 1.7* | 5.6 ± 2.5§§ |
| Speech | 2.2 ± 0.7 | 1.7 ± 0.9 | 1.9 ± 0.8 | 1.9 ± 0.9 | 2.3 ± 0.9 |
| Gait | 2.2 ± 1.0 | 0.6 ± 0.7* | 1.1 ± 0.9* | 1.0 ± 0.8* | 1.3 ± 1.3* |
| Postural stability | 1.7 ± 1.2 | 0.6 ± 0.8* | 0.9 ± 0.8* | 1.0 ± 0.8* | 2.1 ± 1.4§§ |
| Efficacy of combined treatment on motor symptoms | | | | | |
| Total | 24.5 ± 9.2 | 21.3 ± 12.1* | 22.9 ± 9.5* | 21.4 ± 11.3* | 26.9 ± 10.2* |
| Resting tremor | 1.1 ± 2.6 | 0.3 ± 0.8* | 0.1 ± 0.3* | 0.1 ± 0.5* | 0.1 ± 0.2* |
| Postural tremor | 1.9 ± 1.9 | 1.2 ± 1.1* | 0.2 ± 0.5* | 0.9 ± 1.1* | 2.0 ± 1.7*,§§§§ |
| Rigidity | 5.7 ± 3.3 | 5.2 ± 4.1* | 4.9 ± 3.0* | 3.3 ± 2.9*,§ | 3.7 ± 2.2*,** |
| Upper limb akinesia | 6.7 ± 3.9 | 6.1 ± 4.3* | 6.9 ± 4.5* | 6.4 ± 4.2* | 8.0 ± 3.1* |
| Lower limb akinesia | 2.1 ± 1.8 | 1.9 ± 2.3* | 2.3 ± 1.8* | 2.4 ± 2.0* | 2.7 ± 1.7* |
| Bradykinesia | 1.1 ± 1.0 | 1.0 ± 0.9* | 1.0 ± 0.8* | 0.8 ± 0.6* | 1.7 ± 0.8*,§§§§§ |
| Total axial | 3.1 ± 2.4 | 2.3 ± 1.2* | 3.5 ± 1.8* | 3.7 ± 2.2* | 4.7 ± 2.3*,** |
| Speech | 1.3 ± 0.7 | 1.4 ± 0.9*,** | 1.9 ± 0.9 | 1.7 ± 1.1 | 2.2 ± 1.0*** |
| Gait | 0.9 ± 1.0 | 0.5 ± 0.6* | 0.8 ± 0.8* | 1.1 ± 0.8* | 0.9 ± 1.1* |
| Postural stability | 0.9 ± 1.0 | 0.5 ± 0.6* | 0.8 ± 0.7* | 0.9 ± 0.8* | 1.7 ± 1.2*** |

Each postoperative assessment has been compared to baseline (either OFF or ON medication); in addition, 5- and 8-year conditions have been compared.
*$P < 0.001$ compared to medication OFF at baseline.
**$P < 0.05$ compared to medication ON at baseline.
***$P < 0.01$ compared to medication ON at baseline.
§$P < 0.001$ compared to medication ON at baseline.
§§$P < 0.05$ compared to medication OFF at 5 years.
§§§$P < 0.01$ compared to medication OFF at 5 years.
§§§§$P < 0.05$ compared to medication ON at 5 years.
§§§§§$P < 0.01$ compared to medication ON at 5 years.

and did not have a clinically meaningful effect on daily living activities. Comparisons of 8- versus 5-year scores on cognitive variables only revealed a significant decline in an episodic memory task (immediate recall of the RAVLT) (Table 3).

The individual postoperative changes (zeta scores) on cognitive and behavioural variables at 5- and 8-year follow-up are reported in Supplementary Table A. Eight years after surgery, on various cognitive variables (RPM '47, number of correct criteria and total errors on the MWCST, letter verbal fluency, immediate and delayed recall of the RAVLT, and digit span forward), the percentage of patients that declined was clearly higher than the percentage of patients who remained stable or improved. Furthermore, we analysed the raw scores adjusted for age and educational level on those cognitive variables (letter verbal fluency task, immediate and delayed recall of RAVLT episodic memory task, RPM '47 and number of correct criteria on the MWCST) in which there was a statistically significant decline 8 years after surgery, compared to baseline. At 8-year follow-up, on the letter verbal fluency task, 13 patients (81.2%) performed in the normal range, 2 patients (12.5%) performed below the normal range and 1 patient (6.2%) scored around the cut-off score. On the immediate recall of RAVLT, 12 patients (75%) performed in the normal range, 3 patients (18.7%) performed below the normal range and 1 patient scored around the cut-off score (6.2%). On the delayed recall of RAVLT, 13 patients (81.2%) performed in the normal range and 3 patients (18.7%) performed below the normal range. On the RPM '47, 15 patients (93.7%) performed in the normal range and 1 patient (6.2%) scored around the cut-off score. As to the number of correct criteria on the MWCST, 9 patients (60%) performed in the normal range, while six patients (40%) performed below the normal range.

We further analysed UPDRS motor items ON and OFF medication conditions, LEDD and total electrical energy delivered according to the 8-year individual cognitive outcome assessed by means of zeta scores (decline compared to unchanged or improved performance) for various cognitive variables (Supplementary Table B). In individual patients who declined on WCST (total errors) compared to patients with unchanged or improved performance, there were significantly higher scores on the total UPDRS motor score and postural stability in both ON and OFF conditions, and upper

**Table 3 Results obtained on cognitive and behavioural variables in patients at baseline and at 5- and 8-year follow-up**

| Test (range) | Baseline | 5 years | Variation versus baseline (%) | 8 years | Variation versus baseline (%) | Variation versus 5 years (%) |
|---|---|---|---|---|---|---|
| MMSE (0–30) | 26.7 ± 2.7 | 27.1 ± 2.1 | +0.5 | 25.7 ± 4.3 | −4.2 | −5.4 |
| RPM '47 (0–36) | 28.4 ± 5.2 | 26.2 ± 5.7 | −11.6* | 25.7 ± 6.4 | −15.0** | −4.4 |
| RAVLT: immediate recall (0–75) | 39.5 ± 12.6 | 37.0 ± 14.2 | −7.1 | 30.6 ± 10.9 | −18.5** | −19.0* |
| RAVLT: delayed recall (0–15) | 8.6 ± 3.9 | 7.7 ± 3.8 | −18.3* | 5.9 ± 3.3 | −26.2** | −12.8 |
| Digit span forward | 5.6 ± 1.0 | 5.3 ± 1.1 | −5.7 | 5.1 ± 1.1 | −6.9 | −0.02 |
| Digit span backward | 3.75 ± 0.9 | 3.8 ± 1.8 | −2.5 | 3.6 ± 1.2 | −3.6 | +0.5 |
| Corsi's span forward | 4.7 ± 1.1 | 4.6 ± 1.0 | −4.8 | 4.3 ± 0.9 | −2.4 | −0.7 |
| Corsi's span backward | 4.1 ± 1.2 | 3.5 ± 1.1 | −10.3 | 3.7 ± 1.0 | −8.6 | +14 |
| Letter verbal fluency | 32.4 ± 13.1 | 23.5 ± 8.6 | −30.7* | 21.3 ± 8.8 | −29.8** | +3.8 |
| MWCST: correct criteria (0–6) | 4.7 ± 1.7 | 4.0 ± 1.8 | −4.6 | 3.4 ± 2.1 | −24.5* | −20.5 |
| MWCST: total errors (0–48) | 11.1 ± 11.2 | 14.2 ± 9.9 | −79.8 | 17.4 ± 12.7 | +194.8 | +96.5 |
| MWCST: perseverative errors (0–48) | 5.7 ± 4.3 | 4.4 ± 4.9 | −30.5 | 6.6 ± 6.0 | +61.0 | +123.3 |
| Zung's depression scale (20–80) | 46.7 ± 8.5 | | | 43.3 ± 11.0 | | |
| Zung's anxiety scale (20–80) | 43.1 ± 10.6 | | | 39.7 ± 12.2 | | |

Values are mean ± SD.
*$P < 0.05$; **$P < 0.01$.
MMSE = Mini Mental State Examination.

and lower limb akinesia OFF medication (Fig. 1). In individual patients who declined on RAVLT (delayed recall) compared to patients with unchanged or improved performance, there were significantly higher scores on total UPDRS motor score and bradykinesia in both ON and OFF medication conditions, while in individual patients who declined on digit span forward compared to patients with unchanged or improved performance, there were significantly higher scores on gait in both ON and OFF medication conditions. Further significant effects on other cognitive variables are reported in Supplementary Table B.

Eight years after surgery, no significant change was observed on scales assessing depression or anxiety, compared to baseline (Table 3); on these letter variables, according to the individual postoperative changes (zeta scores), the percentage of patients who improved was clearly higher than the percentage of those who worsened (Supplementary Table A).

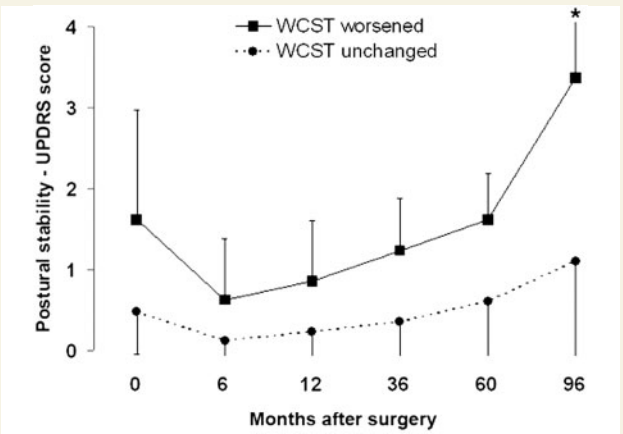


**Figure 1** In individual patients who declined on WCST (total errors) compared to patients with unchanged or improved performance, there were significantly higher scores on postural stability ON medication at the last follow-up visit.

## Features associated with axial impairment

The patients who had worsening of axial symptoms 8 years after implant were compared with those who had stable axial conditions, in order to identify potential categorical features and variables related to poor axial outcome.

## Gait impairment

The comparison of patients who had a significant worsening of gait at 8 years with those who did not, revealed higher baseline scores of UPDRS-III item 29 (gait) in the OFF medication condition, greater amounts of medication after implant (+90.7% at 6 months, $P < 0.05$; +96.8% at 1 year, $P < 0.05$; +246.1% at 3 years, $P < 0.001$; +186.6% at 5 years, $P < 0.001$) and higher energy delivery during the first year after implant (142.1 ± 57.7 versus 95.7 ± 23.4 μJ at 6 months, $P < 0.05$; 136.3 ± 40.6 versus 104.9 ± 20.7 μJ at 1 year, $P < 0.05$).

On the last evaluation visit, patients with gait impairment scored worse on overall rigidity (7.4 ± 2.7 versus 4.4 ± 2.5, $P < 0.05$) and lower limb akinesia (4.8 ± 1.6 versus 3.0 ± 1.8, $P < 0.05$) in the OFF medication condition. These patients also had poorer performance at 5 years on RAVLT delayed recall (4.2 ± 3.4 versus 9.6 ± 3.4, $P < 0.05$) and more perseverations at MWSCT (10.5 ± 7.8 versus 2.7 ± 3.0, $P < 0.05$).

## Postural stability impairment

A retrospective analysis of patients who had a significant worsening of postural stability at 8 years, compared with those who did

not, revealed significantly higher baseline scores of UPDRS-III item 30 (postural stability) (both in the OFF and in the ON medication condition) and significantly greater intake of medication at baseline (Table 4). There were no distinctive baseline cognitive features in this group of patients. On the last evaluation visit, there were no significant differences in UPDRS motor scores except for the postural stability item either in the OFF (1.2 ± 0.8 versus 3.6 ± 0.5, $P < 0.001$) or in the ON medication condition (1.3 ± 0.9 versus 2.4 ± 1.4, $P < 0.05$).

## Medication dosage and energy delivery

The mean preoperative LEDD (1418.2 ± 782.8 mg) was reduced by 58.2% at 5 years and by 60.3% at 8 years. Two patients did not take any dopaminergic medication 8 years after implant, five patients took only dopamine agonists, one patient only took levodopa and the remaining 14 took a combined treatment. No patient was on apomorphine or enteric levodopa.

There were mild variations of stimulation settings (amplitude, pulse width and frequency) after implant, resulting in changes of energy delivered at 6 and 18 months. At 5 years, there was a steep increase of total electrical energy delivered, which later remained stable until 8 years after implant.

Between 5 and 8 years after implant, the patients underwent on average of 9.2 ± 5.2 changes of stimulation settings. Most of these consisted of voltage increases (Table 5) required to guarantee adequate motor control by DBS; this strategy was successful in 90.5% of sessions. Other changes involved the decrease of stimulation frequency or the configuration of active contacts and were aimed at the management of side-effects or worsening of axial symptoms (Table 5). Decreasing the frequency of stimulation improved speech or gait in 64.3% of cases, but occasionally resulted in worsening of tremor. On the other hand, increasing the frequency was efficacious in controlling tremor in 55.6% of sessions.

Seven patients had two Itrel-II/Soletra implantable pulse generators and 13 had a Kinetra. They were all subject to at least one implantable pulse generator change due to duration of battery life; seven patients had two implantable pulse generator changes and one patient had three. On average, the replacement rate per patient was 1.4 ± 0.5 (Itrel-II/Soletra) and 1.5 ± 0.7 (Kinetra) over 8 years. The mean duration of the implantable pulse generator battery was 55.8 ± 4.0 months for Itrel-II/Soletra and 54.4 ± 10.1 for Kinetra.

**Table 4 Correlation between demographic and baseline clinical features with gait and postural stability outcome at 8 years**

| Preoperative features | Gait | | Postural Stability | |
|---|---|---|---|---|
| | Preserved | Worsened | Preserved | Worsened |
| Demographic | | | | |
| Age (years) | 55.8 ± 9.1 | 58.2 ± 4.1 | 55.5 ± 6.2 | 59.6 ± 8.7 |
| Disease duration | 14.0 ± 5.5 | 13.4 ± 4.0 | 13.2 ± 3.9 | 14.9 ± 6.4 |
| Therapy | | | | |
| LEDD | 1224.9 ± 557.5 | 1654.4 ± 976.0 | 1148.6 ± 570.7* | 1918.9 ± 916.0* |
| Motor status | | | | |
| Total motor score | | | | |
| OFF | 59.7 ± 7.4 | 59.1 ± 12.2 | 58.7 ± 8.1 | 60.9 ± 12.5 |
| ON | 23.5 ± 8.4 | 25.7 ± 10.4 | 23.1 ± 8.7 | 27.1 ± 10.1 |
| Gait | | | | |
| OFF | 1.8 ± 0.8* | 2.7 ± 1.0* | 2.2 ± 0.8 | 2.3 ± 1.3 |
| ON | 0.8 ± 1.3 | 0.9 ± 0.6 | 0.6 ± 0.7 | 1.3 ± 1.4 |
| Postural stability | | | | |
| OFF | 1.4 ± 1.0 | 2.0 ± 1.3 | 1.2 ± 1.0* | 2.4 ± 1.1* |
| ON | 1.0 ± 1.2 | 0.8 ± 0.7 | 0.5 ± 0.7* | 1.6 ± 1.1* |
| Cognitive variables | | | | |
| MMSE | 26.9 ± 2.1 | 26.0 ± 3.7 | 27.5 ± 2.5 | 24.8 ± 2.7 |
| RAVLT: immediate recall | 37.8 ± 13.6 | 41.7 ± 10.5 | 41.6 ± 12.0 | 35.3 ± 12.6 |
| RAVLT: delayed recall | 7.8 ± 4.5 | 9.7 ± 2.4 | 8.5 ± 4.0 | 8.7 ± 3.8 |
| Verbal fluency | 32.3 ± 14.6 | 32.6 ± 11.1 | 31.9 ± 10.6 | 33.4 ± 18.6 |
| MWSCT: category | 5.1 ± 1.7 | 3.8 ± 1.7 | 4.9 ± 1.5 | 4.3 ± 2.4 |
| MWSCT: perseveration | 19.7 ± 37.3 | 39.5 ± 48.7 | 31.3 ± 44.3 | 25.0 ± 43.6 |
| MWSCT: total error | 8.4 ± 10.7 | 17.3 ± 11.0 | 10.3 ± 10.4 | 13.0 ± 14.4 |
| Psychiatric variables | | | | |
| Zung anxiety | 50.1 ± 24.2 | 65.7 ± 31.4 | 60.1 ± 28.9 | 52.8 ± 28.4 |
| Zung depression | 58.4 ± 21.0 | 62.7 ± 30.8 | 61.6 ± 26.5 | 58.4 ± 25.1 |

ON and OFF refer to medication status. Statistics refer to the comparison between patients who displayed gait or postural stability impairment at 8 years and patients who did not.
*$P < 0.05$.
MMSE = Mini Mental State Examination.

**Table 5 Number of individual setting changes performed during the reprogramming sessions between 5 and 8 years**

| Changes of: | Motor signs | | | Dyskinesias | | | Dysarthria | | | Freezing | | | Instability | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | + | = | − | + | = | − | + | = | − | + | = | − | + | = | − |
| Stimulating contacts* | 11 | 4 | 6 | 1 | | 1 | 5 | | 7 | 3 | | 4 | 1 | | 1 |
| Continuous/cyclic** | 4 | 2 | | 2 | | 3 | 2 | | | 1 | | 2 | | | 1 |
| Amplitude | 18 | | 1 | | | 1 | 1 | 2 | | | | | | | |
| Pulse width | | | 1 | | | 1 | | | | | | | | | |
| Frequency | 4 | 2 | 2 | 2 | | | 4 | 2 | 1 | 1 | | 1 | 1 | | |

Clinical features have been classified as improved (+), unchanged (=) or worsened (−) following each category of change.
*Encompasses the change from a monopolar active contact to another or to double monopolar configuration or the change from a monopolar to bipolar configuration.
**Encompasses the shift from continuous to cyclic stimulation or vice versa.

## Safety and tolerability profile

No serious adverse events (e.g. haemorrhage, infection or infarction) occurred during surgery. All adverse events that occurred during the study period, including neurological, psychiatric and other events, are listed in Table 6.

Hypophonia was the most frequent motor side-effect; it occurred in nine cases and was associated with dysarthria in three; in four cases dysarthria was not accompanied by hypophonia and one patient was anarthric. Several patients displayed dystonic features, such as eyelid opening apraxia, blepharospasm, oro-mandibular and limb dystonia. In some cases, dystonia was stimulation induced and easily managed by reducing the amplitude; in most cases, however, a treatment with botulinum neurotoxin was required.

All patients gained weight after surgery and this was troublesome in seven patients. The average weight of the whole sample was $66.2 \pm 13.5$ kg before surgery and increased at the 8 year visit to $75.1 \pm 14.6$ kg ($P < 0.001$).

Device-related adverse events were recorded in a minority of patients (Table 6). Four patients suffered a minor skin dehiscence along the cable course in the neck region due to bacterial infection, which was resolved by antibiotic treatment.

Out of 32 (15.6%), 4 patients underwent the removal of one electrode. They experienced a sudden severe decrease of the therapeutic efficacy of STN stimulation and quickly recovered after re-implant. In two cases, the explants were performed early after implant (15 days and 6 months, respectively) and in two later on (11 and 14 months, respectively). In three patients, the removed electrodes had migrated outside the STN, whereas in one patient one electrode was removed due to a local infection.

Unexplained switching-off occurred in one Itrel-II and one Kinetra; these events required emergency management of two patients, due to the reappearance of a severe rebound parkinsonism, with worsening of axial symptoms (postural instability and freezing with falls) and rest/postural tremor.

**Table 6 Adverse events observed in the 20 patients who completed the study and in the 12 patients who failed to complete it**

| Number of patients | Completed the study *n* (%) 20 | Dropped out of the study *n* (%) 12 | Total *n* (%) 32 |
|---|---|---|---|
| Transient | | | |
| Increased sexuality | 2 (10) | 2 (16.7) | 4 (12.5) |
| Manic psychosis | 3 (15) | 0 | 3 (9.4) |
| Apathy | 2 (10) | 1 (8.3) | 3 (9.4) |
| Headache | 1 (5) | 0 | 1 (3.1) |
| Hemiparesis | 1 (5) | 0 | 1 (3.1) |
| Seizure | 1 (5) | 0 | 1 (3.1) |
| Persistent | | | |
| Hypophonia | 9 (45) | 3 (25) | 12 (37.5) |
| Dysarthria | 7 (35) | 2 (16.7) | 9 (28.1) |
| Anarthria | 1 (5) | 0 | 1 (3.1) |
| Dysphagia (mild) | 1 (5) | 0 | 1 (3.1) |
| Blepharospasm | 4 (20) | 0 | 3 (9.4) |
| Eyelid opening apraxia | 9 (45) | 1 (8.3) | 10 (31.2) |
| Oral district dystonia | 3 (15) | 0 | 3 (9.4) |
| Limb dystonia | 3 (15) | 1 (8.3) | 4 (12.5) |
| Apathy | 4 (20) | 1 (8.3) | 5 (15.6) |
| Depressive symptoms | 5 (25) | 0 | 5 (15.6) |
| Increased sexuality | 1 (5) | 0 | 1 (3.1) |
| Psychosis | 4 (20) | 0 | 4 (12.5) |
| Dementia | 1 (5) | 0 | 1 (3.1) |
| Troublesome weight gain | 7 (35) | 3 (25) | 10 (31.2) |
| Stimulation induced | | | |
| Hypophonia | 1 (5) | 0 | 1 (3.1) |
| Limb dystonia | 2 (10) | 0 | 2 (6.2) |
| Unilateral blepharospasm | 0 | 1 (8.3) | 1 (3.1) |
| Buccinators spasm | 2 (10) | 0 | 2 (6.2) |
| Device related | | | |
| Skin dehiscence or infection of components | 3 (15) | 1 (8.3) | 4 (12.5) |
| Lead migration | 3 (15) | 1 (8.3) | 4 (12.5) |
| Unexplained switching-off | 2 (10) | 0 | 2 (6.2) |
| Unrelated to procedure or stimulation | | | |
| Severe spinal arthrosis | 3 (15) | 0 | 3 (9.4) |
| Transitory ischaemic attack | 2 (10) | 0 | 2 (6.2) |
| Cardiac arrhythmia | 0 | 1 (8.3) | 1 (3.1) |
| Cardiac ischaemia | 1 (5) | 0 | 1 (3.1) |
| Cardiac decompensation | 1 (5) | 0 | 1 (3.1) |
| Pulmonary embolism | 0 | 1 (8.3) | 1 (3.1) |
| Death | 0 | 3 (25) | 3 (9.4) |

The table reports the number of patients with adverse events and the percent incidence.

# Discussion

This prospective study reports the long-term follow-up of a cohort of patients with Parkinson's disease who received continuous STN bilateral stimulation for 8 years. We found that the overall motor outcome reported at 5 years was only partly retained 3 years later,

with differential effects on various motor features, whereas cognitive outcome and safety were retained at 8 years.

## Long-term motor outcome

The 55.5% motor improvement achieved by this series of patients at 5 years fits well with earlier 5-year reports (Krack *et al.*, 2003; Schupbach *et al*., 2005; Piboolnurak *et al*., 2007; Wider *et al*., 2007; Gervais-Bernard *et al.*, 2009; Romito *et al.*, 2009; Simonin *et al.*, 2009). In keeping with these studies, we observe here that the majority of parkinsonian motor features, but not speech or postural stability, improved at this time point. Eight years after implant, DBS still provided a sizable reduction of motor impairment compared to baseline, but was less effective compared to 5 years after implant. Cardinal motor signs, such as rigidity and resting tremor, were still adequately controlled by stimulation; gait was also improved in this cohort of patients who had no levodopa-resistant gait impairment (Stolze *et al*., 2001). Speech was not improved by DBS, but did not decline further compared to previous evaluations. In spite of subtle worsening (about 10%) of motor features, a dramatic impairment in functional state emerged after the fifth year of stimulation. This observation is in keeping with a different impact of specific motor features (such as limb akinesia and postural stability) on patients' functionality in everyday life (Schrag *et al*., 2000), as captured by the UPDRS activities of daily living, which is mainly weighted for tasks requiring manual dexterity or axial motor functioning (Fahn *et al*., 1987).

The observation of a decay of outcome in the long-term course of Parkinson's disease, some time around 8 years after STN implant, poses new intriguing issues.

It is possible that the efficacy of STN stimulation decays in the long term. The chronic reduction of daily doses of dopaminergic medication (on average, ~60%) following the implant might be involved in such decrease of efficacy of STN-DBS over time. However, this possibility seems unlikely in view of the observation that when levodopa was acutely administered, rigidity and upper limb akinesia improved significantly, while the remaining motor features did not. This is consistent with the observation that a supra-threshold dose of levodopa does not provide additional benefit to implanted patients (Schupbach *et al*., 2005; Piboolnurak *et al*., 2007) and suggests that disease progression is the main cause of loss of treatment efficacy. STN-DBS is a symptomatic treatment with no efficacy on disease progression, as demonstrated by functional imaging studies (Hilker *et al*., 2005).

It is possible that the implementation of strict inclusion criteria may have contributed to the selection of a subset of patients with Parkinson's disease with faster disease progression than average. Long-term observational studies of patients under medical treatment have documented that, after an average disease duration of 17 years, levodopa remains efficacious for rigidity and tremor, whereas akinesia, gait disorder or postural instability worsen despite treatment (Klawans 1986; Bonnet *et al*., 1987). In the present study, patients had on average 21 years of disease duration at the time of the 8-year evaluation, suggesting that symptoms unresponsive to medical treatment (and possibly also to STN-DBS) have probably appeared. In particular, the onset of axial symptoms could reflect the spreading of neurodegenerative processes to non-dopaminergic neurons (Braak and Del Tredici, 2008; Devos *et al*., 2010). The patients included in this study had very homogeneous baseline features (with no axial impairment in the medication ON state) and a pre-surgery disease duration comparable with that reported in a recent meta-analysis of 22 STN-DBS studies (Kleiner-Fisman *et al.,* 2006). This may indicate that the waiting time before STN implant was too long to allow for remarkable long-term post-implant benefits.

The results of the present long-term study support the possibility that STN implants may be performed earlier than currently suggested. Practice parameters propose to offer surgery to patients only when medical therapy has failed and all other options have been exhausted (Lang *et al.*, 2006). It has been observed that STN-DBS implants performed earlier in the disease course (on average 6.9 years from onset) provide motor and functional improvement during short-term observation (Schupbach *et al*., 2007). Our long-term findings suggest that the global benefit of STN-DBS is partly decreased later in the course of the disease, due to progression of Parkinson's disease and the appearance of medication- and stimulation-resistant symptoms.

The delayed impairment of postural stability is a new finding that partially confirms previous medium-term reports (Krack *et al*., 2003; Piboolnurak *et al*., 2007; Romito *et al*., 2009). The acute administration of a supra-threshold dose of levodopa did not improve postural stability at 8 years in this study. This finding supports the synergic effect of DBS and levodopa in improving postural stability shown by earlier short-term studies (Bejjani *et al*., 2000*b*; Welter *et al*., 2002; Herzog *et al*., 2003) is lost at 8 years.

Long-term observation allowed the detection of individual variability in postoperative motor outcome. In particular, postural stability showed different outcomes in different patients; approximately half were severely affected at 8 years, whereas the others displayed a preserved stability, as revealed by a score of $\leq$2 on the relevant UPDRS item in the best motor condition (with both stimulation and medication). The reasons for this late and inconsistent worsening of stability are not currently known. As suggested by our retrospective analysis reported in Table 4, the subgroup of patients who developed a remarkable worsening of postural stability at 8 years did show a significantly more marked postural instability (as measured by UPDRS-III item 30) at baseline (before surgery) in both the OFF medication and ON medication conditions, and showed a significantly greater intake of antiparkinsonian mediation at baseline. A deleterious effect of STN-DBS on postural stability has been objectively shown very early after surgery (Guehl *et al*., 2006). It has been postulated that microlesions or STN stimulation could interfere with neuronal pathways lying near the STN and involved in postural control (Russmann *et al*., 2004). Accordingly, the inter-individual variability outcome in different patients could reflect the variability of individual physiologic reserve, as determined by ageing processes (Russmann *et al*., 2004). In the present study, performance on the MWCST, assessing frontal executive functions, correlated significantly with postural stability, suggesting a strong interplay between axial motor deterioration and cognition (Yogev *et al*., 2005; Giladi and Hausdorff, 2006; Amboni *et al*., 2008). Among

frontal cognitive functions, divided attention allows carrying out two tasks simultaneously. Previous studies have suggested that a dual task interference on postural control occurs in parkinsonian patients during cognitive (Morris *et al*., 2000; Ashburn *et al*., 2001) and motor tasks (Marchese *et al*., 2003). It has been suggested that patients with Parkinson's disease use attentional strategies to compensate for their balance problems due to dysfunction of basal ganglia circuits (Morris *et al*., 2000). It might be postulated that in patients with Parkinson's disease who have executive dysfunction, the attentional control is less effective and the balance problems tend to be more marked.

## Long-term cognitive and behavioural outcome

As compared to 5 years, the 8-year neuropsychological assessment showed a slight worsening of cognition. The most prominent feature was a decline in the letter verbal fluency task, associated with a significant but slight decline in tasks of abstract reasoning (RPM '47), episodic memory (immediate and delayed recall of RAVLT) and executive function (number of correct criteria on the MWCST). One patient developed dementia 5 years after surgery, which had progressed at 8 years. Thus, there was a 5% incidence of dementia in our sample, in keeping with 6% reported in another 5-year follow-up study (Krack *et al.*, 2003) that also implemented strict selection criteria. These incidence rates are lower than those reported in surveys enrolling cohorts of less strictly selected patients. In one of these latter studies, the cumulative incidence of dementia was 38% over 10 years (Hughes *et al*., 2000).

The observed decline in a letter verbal fluency task 8 years after surgery is in agreement with previous studies reporting a similar decline at different times after implant: 1 year (Ardouin *et al*., 1999; Pillon *et al*., 2000; Daniele *et al.*, 2003), 3 years (Funkiewiez *et al*., 2004), and 5 years follow-up (Contarino *et al*., 2007). Recently, it has been shown that, compared to best medical treatment, patients with STN-DBS implants performed significantly worse on tasks of verbal fluency and on the Stroop test (Witt *et al*., 2008). In this latter study, there was no between-group difference in the rate of psychiatric adverse events. In a previous study from our group, the postoperative decline in verbal fluency was detectable early after STN-DBS and became more evident at 5-year follow-up (Contarino *et al*., 2007). The present study suggests that the decline in verbal fluency detected after 8 years is slightly more pronounced than after 5 years.

Since the decline in verbal fluency has been mostly detected shortly after surgery for STN-DBS, it has been hypothesized that it might be due to surgical microlesions affecting cortical-basal ganglionic circuits involved in word retrieval processes (Troster *et al*., 2003). Alternatively, STN stimulation might result in decreased activation of the inferior frontal and temporal cortex in the left cerebral hemisphere, resulting in decreased verbal fluency (Schroeder *et al*., 2003). Whatever the pathogenic mechanism, decline in verbal fluency remains a common feature of Parkinson's disease, regardless of neurosurgical intervention (Matison *et al*., 1982).

A limitation of the present study and several other previous studies on STN-DBS in Parkinson's disease is the lack of a control group of patients with Parkinson's disease who did not undergo neurosurgery, which should be matched to the STN-DBS Parkinson's disease group at baseline as to clinical and demographic variables (age, educational level, severity of motor impairment and cognitive status). The recruitment of such a medically treated control Parkinson's disease group could allow the assessment of cognitive decline due to Parkinson's disease progression and ageing in the long term, in order to compare the long-term cognitive outcome of medically treated patients with Parkinson's disease versus patients with Parkinson's disease who undergo STN-DBS. Recently, in a naturalistic controlled study with a 3-year follow-up (Zangaglia *et al*., 2009), neuropsychological assessment was carried out in 32 patients with Parkinson's disease who underwent STN-DBS and 33 patients with Parkinson's disease who declined DBS, even though they were eligible for the procedure (Parkinson's disease control group). This study showed that at the 3-year follow-up, performance on a letter verbal fluency task was significantly worse in the implanted group compared to the control group. Depressive symptoms and apathy were reported in 25% of patients in this cohort, although the mean depression score did not change compared to baseline. These symptoms may represent a major issue in short-term studies and might result from the interaction between STN stimulation and dopaminergic drug reduction (Czernecki *et al*., 2008). Remarkably, no patient in this series committed suicide or manifested suicidal intentions (Albanese *et al*., 2005; Voon *et al*., 2008).

## Outcome predictors

The observed variability of outcome in the long-term poses the issue of selecting patients with better chances of long-term benefit. The inter-individual variability of this study could rely on at least three domains: (i) the intrinsic differences between patients at baseline; (ii) the extrinsic differences (mainly lead location, burden of lesion due to the procedure, parameters of stimulation and medication); and (iii) the interaction between these intrinsic and extrinsic differences.

The concept that the clinical benefit induced by STN-DBS is comparable with that observed with levodopa treatment relies on short-term observations (Pollak *et al*., 1996; Charles *et al*., 2002; Pahwa *et al*., 2005). More recent studies report that the preoperative response to levodopa does not predict medium-term improvement following DBS (Piboolnurak *et al*., 2007). In keeping with this evidence, the present study did not reveal a predictive value of preoperative levodopa response. We also observed that few single baseline motor features (such as the UPDRS gait and postural stability scores) and the preoperative LEDD could predict the long-term motor outcome. This indicates that indices of disease severity at baseline may be related to poorer long-term outcome.

## Long-term safety

The outlook on long-term safety of STN-DBS is quite reassuring. Eight years after implant, there was no significant increase of side-effects compared to 5-year observations. Hypophonia, eyelid opening apraxia (observed in 45% of our cohort) and weight gain (35%) were the most frequent side-effects. The pathophysiology of these is still far from being understood; hypophonia has been consistently reported by many groups with a wide ranging prevalence from 4% (Krack *et al*., 2003) to 70% (Piboolnurak *et al*., 2007). Likewise, eyelid opening apraxia was a complication for up to 30% of patients followed up for 5 years (Schupbach *et al*., 2005; Gervais-Bernard *et al*., 2009). Weight gain was judged troublesome in the long-term studies with a prevalence ranging from 20% (Romito *et al*., 2009) to 48% (Piboolnurak *et al*., 2007) and further limited the mobility of these patients even if it could also be the results of reduced mobility itself.

In conclusion, our findings suggest that STN-DBS in patients with Parkinson's disease is an effective procedure to improve levodopa-responsive parkinsonian symptoms and allows the maintenance of a long-lasting reduction of dopaminergic treatment for at least 8 years. STN-DBS is a safe procedure with regards to cognitive and behavioural morbidity over long-term follow-up, when appropriate criteria are used to select candidates for neurosurgery. The late stage decline in motor performance raises important new questions for the timing of performing DBS during the disease course. It has been suggested that neurosurgery performed earlier after the diagnosis of Parkinson's disease may prevent psychosocial degradation and maintain quality of life, especially in young patients facing a long course of disease (Mesnage *et al*., 2002; Schupbach *et al*., 2007). However, STN-DBS can lead to side-effects such as apathy, weight gain or eyelid opening apraxia. So far, there is no consensus on the timing for surgery and the results provided by our study may contribute to define the best trade-off between motor efficacy and deterioration of quality of life. The long-term motor outcome by itself with the appearance of disabling symptoms resistant to medical and surgical therapies may support an anticipation of implants and it should be taken into account in the debate about the optimal timing for surgery.

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# Supplementary material

Supplementary material is available at *Brain* online.

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# Motor and cognitive outcome in Parkinson's disease patients eight years after subthalamic implants

## Supplemental Material Online

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**Abbreviations:** LEDD, levodopa-equivalent daily dose; MMSE, Mini-Mental State Examination; MWCST, Modified Wisconsin Card Sorting Test; RAVLT, Rey's Auditory Verbal Learning Test; RPM '47, Raven's Progressive Matrices ; TEED, total electrical energy delivered; UPDRS, Unified Parkinson's Disease Rating Scale.

**Table A.** The percentage of patients displaying improvement, no change or decline at neuropsychological tests according to the zeta score.

| | Improvement | | | No change | | | Decline | | |
|---|---|---|---|---|---|---|---|---|---|
| | **5 year vs. baseline** | **8 year vs. baseline** | **8 vs. 5 year** | **5 year vs. baseline** | **8 year vs. baseline** | **8 vs. 5 year** | **5 year vs. baseline** | **8 year vs. baseline** | **8 vs. 5 year** |
| **MMSE*** | 10 | 18.75 | 20 | 80 | 62.5 | 40 | 10 | 18.75 | 40 |
| **RPM‘47*** | 0 | 6.25 | 10 | 70 | 37.5 | 40 | 30 | 56.55 | 50 |
| **RAVLT: immediate recall*** | 20 | 0 | 0 | 50 | 68.75 | 60 | 30 | 31.25 | 40 |
| **RAVLT: delayed recall*** | 10 | 0 | 0 | 80 | 62.50 | 60 | 10 | 37.50 | 40 |
| **Digit span forward*** | 20 | 6.25 | 10 | 60 | 62.50 | 60 | 20 | 31.25 | 30 |
| **Digit span backward*** | 20 | 25 | 20 | 60 | 56.55 | 70 | 20 | 18.75 | 10 |
| **Corsi’s span forward*** | 10 | 13.30 | 20 | 70 | 73.30 | 70 | 20 | 13.30 | 10 |
| **Corsi’s span backward*** | 0 | 6.70 | 10 | 80 | 80 | 80 | 20 | 13.30 | 10 |
| **Letter verbal fluency*** | 0 | 0 | 0 | 55.5 | 56.25 | 60 | 45.5 | 43.75 | 40 |
| **MWCST: correct criteria*** | 0 | 0 | 0 | 66.7 | 50 | 40 | 33.3 | 50 | 60 |
| **MWCST: total errors†** | 0 | 0 | 0 | 88.8 | 50 | 40 | 22.2 | 50 | 60 |
| **MWCST: perseverative errors†** | 22.2 | 25 | 30 | 66.7 | 50 | 40 | 11.1 | 25 | 30 |
| **Zung Depression†** | - | 40 | - | - | 40 | - | - | 20 | - |
| **Zung Anxiety†** | - | 40 | - | - | 53.30 | - | - | 6.70 | - |

Abbreviations: *, an increase >1 SD indicates improvement, whereas a decrease >-1 SD indicates decline; †, an increase >1 SD indicates decline, whereas a decrease >1 SD indicates improvement. Zung Depression and Zung Anxiety scales were not performed at 5 year follow-up

**Table B.** Mean UPDRS scores (±SD) according to the cognitive decline displayed by patients at the latest follow-up visit. No statistically significant inter-group difference was found when comparing resting tremor, postural tremor, rigidity, LEDD, and TEED.

| Cognitive profile | | Medication OFF | | | | | | | Medication ON | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | Upper limbs akinesia | Lower limbs akinesia | Bradykinesia | Speech | Gait | Postural stability | Total | Upper limbs akinesia | Lower limb akinesia | Bradykinesia | Speech | Gait | Postural stability |
| **MWSCT (total error)** | = | 26.9 ±9.5[a] | 7.4 ±1.7[c] | 2.2 ±0. 9[c] | 1.5 ±0.9 | 2.0 ±0.9 | 0.6 ±0.9 | 1.1 ±1.4[a] | 23.0 ±7.2[a] | 7.2 ±2.5 | 2.0 ±1.5 | 1.5 ±0.8 | 2.0 ±0.9 | 0.6 ±0.9 | 1.1 ±1.4 |
| | - | 41.2 ±6.7 [a] | 12.4 ±2.0 [c] | 4.4 ±1.7 [c] | 2.2 ±0.5 | 2.5 ±0.8 | 1.5 ±1.5 | 2.7 ±1.2[a] | 32.2 ±7.6[a] | 9.4 ±1.5 | 3.1 ±1.5 | 2.0 ±0.8 | 2.5 ±0.8 | 1.1 ±1.4 | 2.2 ±0.7 |
| **Verbal Fluency** | = | 31.4 ±11.1 | 8.6 ±3.0 | 2. 6 ±1.5[a] | 1.7 ±0.9 | 2.1 ±0.8 | 0.8 ±1.0 | 1.6 ±1.5 | 25.1 ±6.7 | 7.9 ±2.3 | 2.0 ±1.6 | 1.6 ±0.7 | 2.1 ±0.8 | 0. 7 ±0.9 | 1.4 ±1.2 |
| | - | 37.4 ±10.4 | 11.6 ±2.6 | 4.3 ±1.5[a] | 2.1 ±0.7 | 2.4 ±1.0 | 1.4 ±1.6 | 2.4 ±1.4 | 30.9 ±10.1 | 8.9 ±2.3 | 3.3 ±1.4 | 2.0 ±0.8 | 2.4 ±1.0 | 1.1 ±1.5 | 2.0 ±1.1 |
| **RAVLT (delayed recall)** | = | 30.5 ±12.6[a] | 9.4 ±4.2 | 3.1 ±2.0 | 1.6 ±0.8[a] | 1.9 ±0.7 | 0.9 ±1.1 | 1.7 ±1.5 | 23.2 ±6.9[b] | 7.5 ±2.5[a] | 2.2 ±1.7 | 1.3 ±0.5[c] | 1.9 ±0.7 | 0.6 ±0.8 | 1.5 ±1.2 |
| | - | 41.3 ±3.6[a] | 11.7 ±2.3 | 4. 4 ±1.7 | 2.4 ±0.5[a] | 2.6 ±1.0 | 1.3 ±1.5 | 2.3 ±1.4 | 35.1 ±5.3[b] | 10.1 ±1.3[a] | 3.4 ±1.4 | 2.4 ±0.5[c] | 2.6 ±1.0 | 1.1 ±1.5 | 2.0 ±1.1 |
| **MMSE** | = | 33.1 ±11.8 | 9.3 ±3.1 | 3.3 ±1.8 | 1.8 ±0.9 | 2.2 ±0.9 | 1.0 ±1.3 | 1.5 ±1.3[a] | 27.4 ±9.4 | 8.3 ±2.5 | 2.6 ±1.8 | 1.8 ±0.8 | 2.2 ±0.9 | 0.8 ±1.2 | 1.5 ±1.1 |
| | - | 38.0 ±4.4 | 12.3 ±2.5 | 3.7 ±1.1 | 2.0 ±0.0 | 2.3 ±0.6 | 1.3 ±1.5 | 3.7 ±0.6[a] | 28.7 ±5.1 | 8.3 ±1.1 | 2.3 ±0.6 | 1.7 ±0.6 | 2.3 ±0.6 | 1.0 ±1.0 | 2.7 ±1.1 |
| **RPM ‘47** | = | 30.9 ±11.7 | 8.7 ±3.1 | 2.6 ±1.6 | 1.7 ±0.7 | 1.9 ±0.8 | 0.7 ±1.0 | 1.6 ±1.6 | 23.6 ±7.7 | 7.4 ±2.6 | 2.0 ±1.7 | 1.0 ±0.8 | 1.7 ±0.7[a] | 0.6 ±0.9 | 1.5 ±1.3 |
| | - | 37.2±9.7 | 11.0 ±2.9 | 4.0 ±1.6 | 2.0 ±0.9 | 2.6 ±0.7 | 1.4 ±1.5 | 2.2 ±1.4 | 31.6 ±8.0 | 9.2 ±1.5 | 3.1 ±1.4 | 2.0 ±0.8 | 2.7 ±0.7[a] | 1.1 ±1.4 | 1.9 ±1.1 |
| **Digit Span** | = | 33.9 ±11.8 | 10.1 ±3.9 | 3.3 ±1.8 | 1.9 ±0.9 | 2.1 ±0.9 | 0.8 ±0.9[a] | 1.9 ±1.6 | 26.8 ±7.7 | 8.5 ±2.6 | 2.5 ±1.6 | 1.7 ±0.7 | 2.1 ±0.9 | 0.6 ±0.8[a] | 1.6 ±1.3 |
| | - | 39.7 ±6.5 | 11.3 ±1.5 | 4.7 ±2.1 | 2.3 ±0.6 | 2. 3 ±0.6 | 2.3 ±2.1[a] | 2.3 ±0.6 | 34.3 ±11.5 | 9.0 ±1.7 | 3.7 ±2.1 | 2.0 ±1.0 | 2.3 ±0.6 | 2.0 ±2.0[a] | 2.0 ±0.0 |
| **Spatial Span** | = | 33.4 ±11.7 | 9.8 ±3.7 | 3.1 ±1.7 | 1.9 ±0.9 | 2.1 ±0.9 | 1.0 ±1.0 | 1.8 ±1.5 | 26.3 ±7.7 | 8.4 ±2.7 | 2.4 ±1.5 | 1.6 ±0.7 | 2.1 ±0.9 | 0.7 ±0.8 | 1.5 ±1.1 |
| | - | 42.3 ±3.2 | 13.0 ±2.0 | 5.3 ±1.5 | 2.3 ±0.6 | 2.3 ±0.6 | 1.3 ±2.3 | 2.7 ±1.1 | 36.7 ±8.3 | 9.7 ±0.6 | 4.0 ±1.7 | 2.3 ±0.6 | 2.3 ±0.6 | 1.3 ±2.3 | 2.7 ±1.1 |

Abbreviations: =, unchanged; -, worsened; [a], $p<0.05$; [b], $p<0.01$; [c], $p<0.001$.